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THREE CASES OF CONGENITAL CYANOSIS AFFECTING ALL CHILDREN IN A FAMILY AND A NEW METHOD OF DIAGNOSIS OF CONGENITAL HEART LESIONS *

JULIUS H. HESS, M.D., and ROY G. PEARCE, M.D.
CHICAGO

These cases are presented primarily because of the rarity of the same anomaly affecting all children of a family.

The method by which we have arrived at an approximate diagnosis of the nature of the causative factor is presented as a preliminary report.

The three boys, Albert, 11, Theodor, 10, and David, 6 years of age, will in what follows be referred to as Cases 1, 2 and 3, respectively.

These boys, who came under observation two and one-half years ago, during an attack of whooping cough, and who have been under observation ever since, all show an excellent mental development and the two younger ones good physical development. The cyanosis of the skin and mucous membranes is constant and the latter is especially evident in the conjunctival and buccal mucous membranes and in the lips. Their cyanosis increases under various conditions, more especially during periods of excitement following physical overexertion and in the presence of inflammatory conditions of the respiratory tract. The cyanosis decreases on deep voluntary breathing, persisting, however, in the absence of all evidence of bronchial irritation. It differs from the intense blue and purple discoloration, as usually seen in congenital heart cases, and gives the skin a greenish hue, which is especially marked below the eyes and around the nose and mouth, and causes the children to have what might be described as a ghastly appearance.

Case 1.—A boy aged 11 years, with a history of instrumental delivery and a weight of 7 pounds at birth, had been delicate from the beginning. He had his first attack of bronchitis at 1 month with repeated attacks thereafter. His first attack of tonsillitis occurred at the age of 9 months, with subsequent attacks at frequent intervals until his tonsils were removed three years ago. He had pneumonia at 8 years, three months before the cyanosis came on, which was

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* Read before the Section on Diabetes of Children at the Sixty-Seventh Annual Session of the American Medical Association, Detroit, June, 1916.

noted about two and one half years ago, and he had whooping cough in February, 1914. He was intensely cyanotic and appeared desperately ill during the first two weeks of his whooping cough, expectorating much mucus, but not vomiting. A tuberculin skin reaction was first made in 1912 and it was reported as positive. The child is of a nervous temperament. He usually feels well during warm weather, but his bronchitis is aggravated by cold weather and he is generally affected by the cold. He has never had eczema or any other skin lesion.

Case 2.—A boy, aged 10 years, with a history of having been born at full term, noninstrumental, not asphyxiated at birth, and weighing 7 pounds, has always taken cold easily and suffered from repeated attacks of bronchitis. He had eczema at 2 years of age, lasting six months. He had measles at 6 years, and had two attacks of tonsillitis and severe attacks of whooping cough at the same time as his two brothers. Cyanosis is constantly present and practically the same, although less marked than that of the other boys. He is the most robust of the three boys.

Case 3.—A boy, aged 6 years, born at full term, noninstrumental, weighing 9 pounds at birth, had repeated attacks of mild bronchitis and had pneumonia when he was 3 years of age. This was followed by whooping cough at the same time his brothers had it. The last disease was very severe and resulted in marked cyanosis, which was constantly present for about 6 weeks. He had a slight attack of eczema, which mainly involved his hands, when he was 4 years old.

A Summary of the Past History.—The three boys were all continuously cyanotic, all of them were subjects to repeated attacks of bronchitis, two of them had had pneumonia, all had had repeated attacks of tonsillitis, all had suffered severely from whooping cough with prolonged increase of their general cyanosis during the first few weeks of the disease, and two of them had had mild eczema.

Family History.—The mother's personal and family history are entirely negative. The father's personal history and his family history, as obtained for three generations, was negative, except for a possible cardiac disease in a brother of the father, who died when he was 4 years of age.

Clinical Examinations.—An examination of the three boys showed that all were exceptionally bright boys. The patient in Case 1 was delicate and of poor physique, the other two being more robust. Table 1 gives comparative figures as to their general development as compared with boys of similar age.[1]

The cyanosis is more marked in the patients in Cases 1 and 3 than in Case 2 and the latter boy is the best developed physically. It is most marked on the skin of the face, the mucous membrane of mouth, eyes and lips, although the entire body shows more or less cyanosis. There is an absence of clubbing of fingers.

The skin is smooth and soft and presents nothing abnormal, except its color, which is of a greenish hue. The boys were shown before the Western Dermatological Society and the opinion was expressed that the color was not due to a hyperpigmentation of the skin, nor was it thought to be due to any of the various dermatoses, because of the absence of infiltration, hyperkeratosis and scaling. It was thought that the color was subcuticular, the overlying epidermis being perfectly normal, and that the picture presented was not due to a skin condition.

The tuberculin test was positive in Case 1, corroborating the test

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[1] Whipple, G. M.: Manual of Mental and Physical Tests, Part 1.

TABLE 1.—DEVELOPMENT OF THE THREE BOYS AS COMPARED WITH THE NORMAL

	Age, Years	Weight, Lb.	Height, Cm.	Grip Strength, Lb.		Girth Chest, Cm.			Girth 9th Rib, Cm.		Girth Waist, Cm.	Depth Chest, Cm.		Breadth Chest, Cm.	
				R.	L.	Inhal.	Normal	Exhal.	Inhal.	Exhal.		Inhal.	Exhal.	Inhal.	Exhal.
Patient 1.........	11	31.8	136.7	18	17.5	71.1	66.2	64.5	69.8	60.8	63.4	16.6	14.7	22.3	20.2
Average........	11	32.07	137.19	18.85	17.72										
Patient 2.........	9	23	124.6	13	13.5	64.4	60.8	59.8	62.3	57.2	57.3	15.6	13.3	19.9	18.5
Average........	9	26.33	126.1	14.34	13.47										
Patient 3.........	5	18.8	110.2	7.5	7.5	58.1	55.2	54.5	57	53.1	54.9	13.8	12	19	17.3
Average........	5	....	105.9												

made in 1912, and negative in the two younger boys. None of the patients showed any marked glandular enlargement.

Examination of the chest of the boy in Case 1 showed a slight impairment of resonance posteriorly to the left of the spine at the level of the fourth and fifth dorsal vertebrae. Whether this was due to enlarged heart or to peribronchial infiltration was difficult to ascertain. The voice sounds were more distinct over this area and the breath sounds were harsh, with prolonged expiration. Auscultation showed the presence of numerous fine moist râles over both lungs posteriorly on repeated examinations, although not constant. The cardiac area of dulness corresponded with the tele-Roentgen examination. Repeated auscultation of the heart failed to reveal any abnormal findings, except an accentuated second pulmonic sound during the bronchial attacks.

In Case 2 the lungs were negative except for the frequent presence of numerous small, moist râles over both sides posteriorly. There were no abnormal heart sounds and the heart was otherwise negative except for slight enlargement of the cardiac area.

In Case 3 the lung findings were entirely negative except for the frequent presence of fine, moist râles heard over the posterior surface of both lungs.

The roentgenograms in Case 1 showed marked pulmonary findings, indicative of changes in the hilus along the larger trunks of bronchial trees and several areas which might be taken for calcareous deposits. The patient in Case 2 whose picture was taken while he was suffering from severe bronchitis, showed marked infiltration of bronchi, especially of the upper lobes. Case 3 showed very few lung changes.

The Roentgen-ray examination of the heart showed a cardiac enlargement in all three cases, most marked in Case 1. These measurements were made by the tele-Roentgen method, the patient being in the upright position, and were as follows:

HEART DIMENSIONS BY THE TELE-ROENTGEN METHOD, CM.

	Case 1	Normal Children of 131 and 140 cm. Tall (Groedel)
Medium right	3.75	3.08 cm.
Medium left	7	6.79 cm.
Length	11	10.09 cm.

These figures show a diagonal and transverse increase of about 1 cm. over the normal.

HEART DIMENSIONS BY THE TELE-ROENTGEN METHOD. CM.

	Case 3	Normal Children between 102 and 110 cm. Tall (Groedel)
Medium right	3.25	2.55
Medium left	5.5	5.45
Length	9	8.4

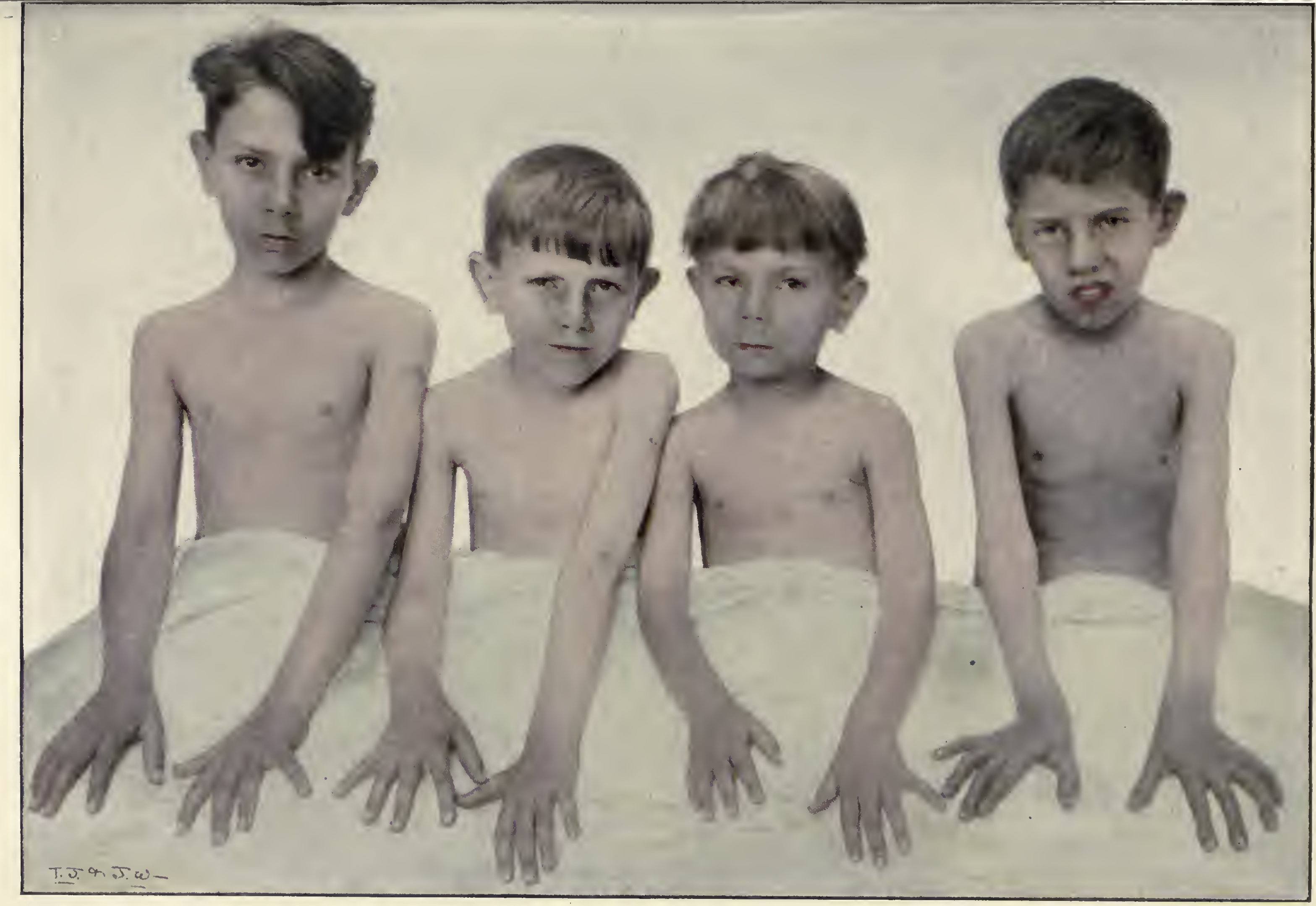

Fig. 1.—At 1, 2 and 3 are illustrated the three cyanotic boys, the only children in this family; all show a constant cyanosis of a greenish hue and are without heart murmurs. At 4 is shown a case of congenital heart disease, giving all the typical findings, including a deep purple cyanosis, a loud murmur and clubbed fingers.

These figures show an increase of 0.75 cm. in the transverse diameter and about 0.5 cm. in the oblique length.

In Cases 1 and 2 Roentgen-ray examination shows a marked prominence of the arch of the pulmonary artery and enlargement of the right heart. The latter might be expected in acquired mitral involvement. This can be excluded by the absence of cardiac murmurs.

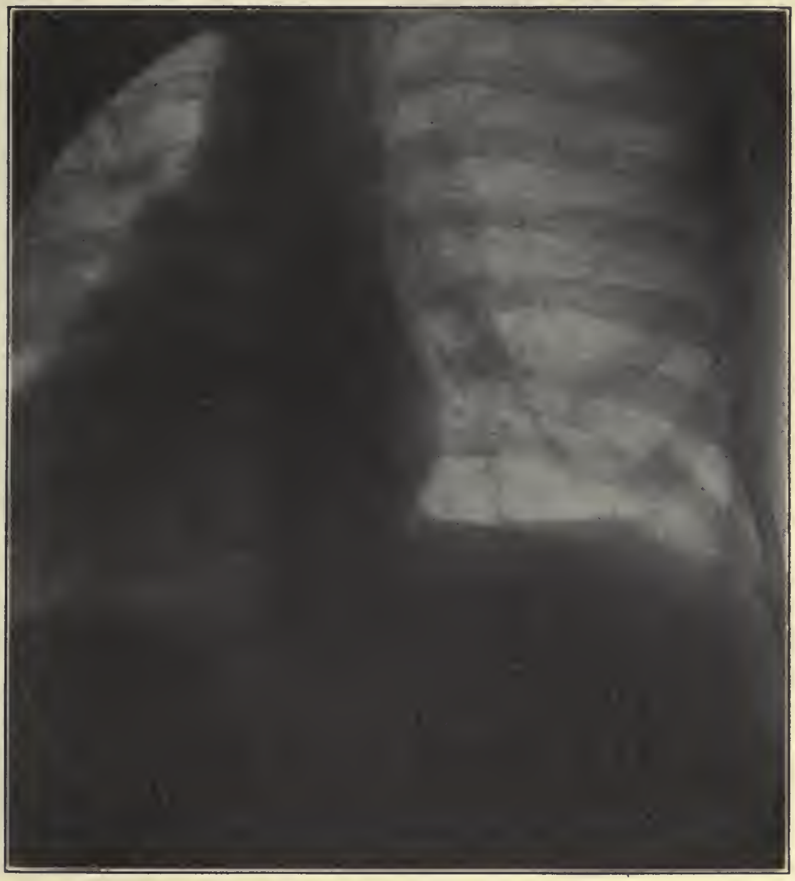

Fig. 2.—Roentgenogram, Case 1.

The pulse and respiration were studied with the polygraph with the following results:

	At Rest		After Severe Exercise	
	Pulse	Respiration	Pulse	Respiration
Case 1	86	24	120	44
Control boy (same size, robust)	80	20	96	27
Case 2	84	24	84	27
			Arrhythmia	
Control boy (frail)	88	22	126	28

In Case 1 and his control it will be noted that both the pulse and respiration rate were higher in the former, and that after severe exercise there was a marked increase in both in Case 1, less so in his control. In Case 2 the control boy had a somewhat higher pulse. This might be accounted for by the fact that he was frail and somewhat anemic. After severe exercise, and this held true for several examinations, neither the pulse nor the respiration rate was noticeably increased in Case 2, but the respirations became deeper and he showed a marked cardiac arrhythmia. His control showed a marked increase in pulse rate, but only a slight increase in the number of respirations. It is difficult to account for the behavior of the pulse and respiration in Case 2 after exercise.

The blood pressure in Cases 1 and 2 and their controls was taken by the auscultatory methods. The following results were obtained:

Blood Pressure in Cases 1 and 2 by Auscultatory Method

	Syst. P.	Diast. P.	Pulse P.	Pulse Rate
Case 1	89	70	19	86
Control	92	66	26	80
Case 2	88	70	18	84
Case 3	70	45	25	84

Judson and Nicholson[2] give the following figures for children of corresponding age, taken by the auscultatory method:

Age, Years	Syst. P.	Diast. P.	Pulse P.	Pulse Rate
11	95.8	62.3	35.5	87
9	91.7	62.2	29.5	84
6	93.8	63.5	30.3	95

It will be noted that in Cases 1 and 2 the pulse pressure was considerably below that of the control and the figures of Judson and Nicholson, showing a lessened peripheral resistance as well as a lessened systolic impulse, as compared with the quoted figures.

The electrocardiograms do not show any great deviation from the normal; however, it will be noted that R is taller in Lead III than in Lead I, while S is deepest in Lead I. This is suggestive of right ventricular hypertrophy. In left ventricular hypertrophy R is usually found tallest in Lead I and shortest in Lead III, while S is deepest in Lead I, the reverse of the above findings. These findings are most marked in Case 2, that of the boy who shows the best general development. In summarizing these findings it may therefore be stated that our electrocardiograms do not vary much from the normal, but indicate a predominance of right-side ventricular activity. Lewis states that if there is one congenital defect in which the electric curves should be normal it is the uncomplicated patency of ductus arteriosus, while marked pulmonary stenosis is usually associated with extreme degrees of right-side hypertrophy, which is amply evidenced in the electrocardiograms, unless decompensation is present.

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[2] Judson and Nicholson: Am. Jour. Dis. Child., 1914, **8**, 257.

It was hoped that the blood findings would show some evidence which would aid in the diagnosis. The hemoglobin was examined by spectrophotometer. The Hüfner instrument was used. By this method the absolute number of grams of hemoglobin per 100 c.c. of blood was determined. Case 1 showed 16.33 gm., as compared with the normal 14.57 gm. for his age. Case 2 showed 14.80 gm., and Case 3, 14.45 gm. as compared with a normal average of 13.28 gm., showing an absolute increase in the hemoglobin content of the blood.

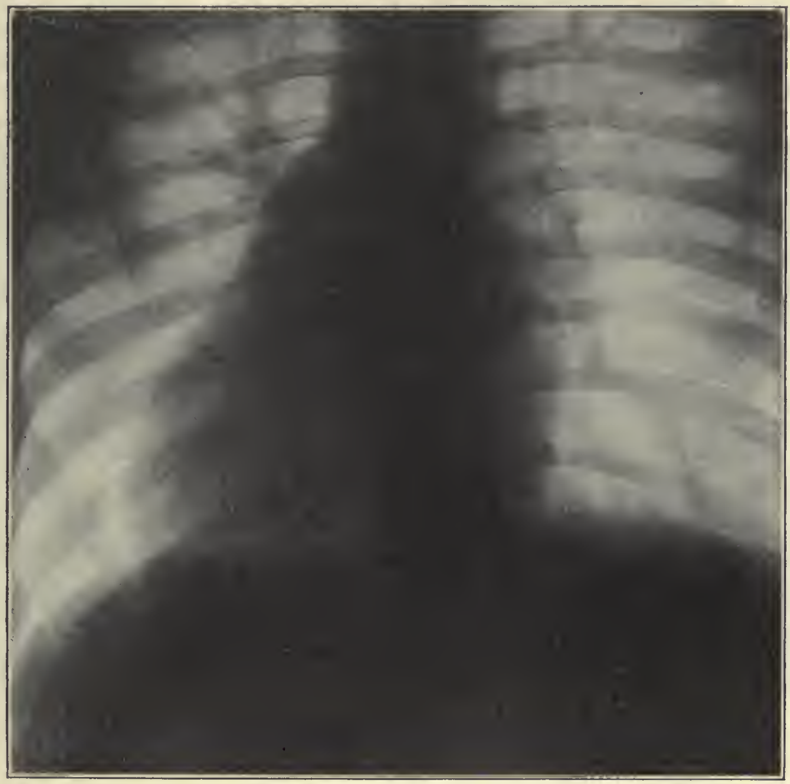

Fig. 3.—Roentgenogram, Case 2.

On spectroscopic examination no band was visible in the red, indicating the absence of appreciable amounts of either methemoglobin or sulphemoglobin. The absorption bands in each of the three cases corresponded to those of oxy-hemoglobin. This would exclude enterogenous cyanosis from further consideration. The examinations were made with Krüss spectroscopic apparatus. Several cubic centimeters of blood were removed from a vein by means of a syringe and placed into twice the volume of distilled water. The solution was then filtered.

The filtrate was placed into a cell for observation of the absorption bands in the spectroscope. Distilled water was added until good transmission of only the red light was obtained. The addition of phenylhydrazin, which has a tendency to intensify the sulphemoglobin band in the red, failed to bring out any such band in these solutions.

The resistance of the red blood corpuscles was tested by a slight modification of that of Limbeck and Hamburger. Small amounts of the washed corpuscles are placed in varying concentrations of sodium chlorid solution from 0.3 per cent. to 0.75 per cent., incubated for two hours and then the beginning and end points of hemolysis read. The figures were well within the normal limits; that of Case 1 beginning at 0.375 per cent. and completed at 0.325; Case 2 beginning at 0.4 and complete at 0.325, and Case 3 beginning at 0.4 and complete at 0.35.

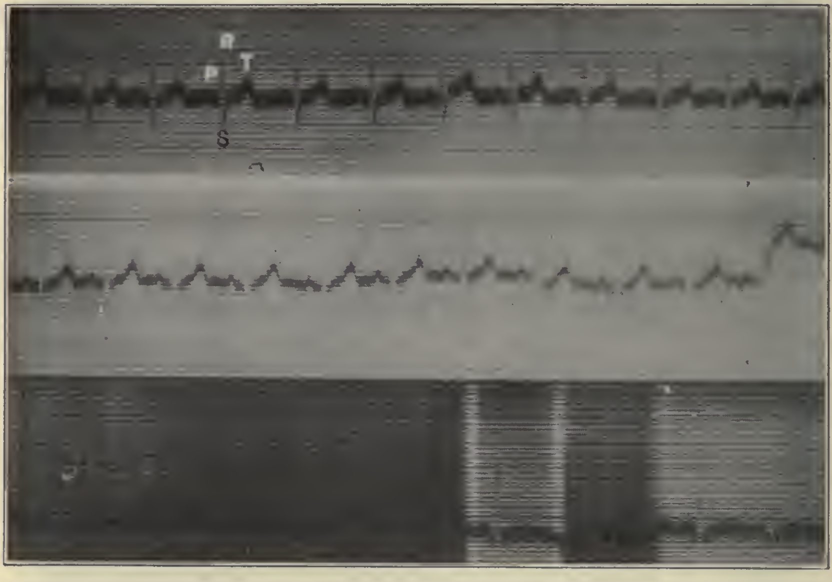

Fig. 4.—Electrocardiograms taken in Case 2. Upper, Lead I; middle, Lead II; lower, Lead III.

The Duboscq colorimeter failed to show any abnormal pigment in the plasma when compared to normal plasma.

Further examination of the blood showed the following:

	Case 1	Case 2	Case 3
Erythrocytes	3,900,000	4,280,000	4,100,000
Leukocytes	6,800	12,400	12,900
Differential	Per Cent.	Per Cent.	Per Cent.
Lymphocytes	42	34	39
Large Mononuclears	3	1	4
Neutrophils	50	61	52
Transitionals	1	2	2
Eosinophils	2	2	3
Basophils	2		

The red cells showed no degenerative changes, were about normal in number and shape, somewhat enlarged, were deeply colored, contained an excessive amount of hemoglobin, as shown by the spectrophotometer, and their resistance was normal. The white cells showed comparatively normal average and total count in Cases 2 and 3, somewhat less so in Case 1. This upholds the idea that there is absence of blood concentration. The differential counts were normal in Cases 2 and 3 with a somewhat higher lymphocyte count in Case 1; the total leukocyte count and high lymphocyte percentage in Case 1 may have a relationship to the positive tuberculin reaction in this case.

The temperature of the boys averaged about 37.4 C.

The liver at no time showed evidence of any marked degree of enlargement. This holds true during the repeated attacks of bronchitis and during the whooping cough.

The spleen was never palpable in any of the cases.

The urine was always negative to tests for albumin, sugar, and acetone and never contained more than traces of indican. Blood, pus and casts were never found.

The feces showed a normal bacterial flora and an absence of parasites. At no time was there a protracted constipation.

Impaired circulation through the tissues might account for the cyanosis. Therefore we measured the volume of blood flow through the hands by the Stewart method. His method depends on the principle that the heat given off by the hand at rest is derived entirely from the circulating blood. Knowing the temperature of the arterial blood, the temperature of venous blood and the number of calories given off in a given time, we can calculate the amount of blood that must have flowed in a given area. By this method it was determined that in Case 1 there was a blood flow of 10.9 c.c. a minute per 100 gm. of hand, a figure well within normal limits and almost twice as high as was obtained at the same time under the same conditions from a healthy boy of the same age. Normal figures for the adult, as quoted by Lowey and Schröter,[3] are 6.4 c.c. per 100 gm. per minute; according to Pletsch[4] 3.9 to 8.8 c.c. per minute, the average being 6.12 c.c. per minute; according to Hewlett[5] and his co-workers between 2 c.c. and 8 c.c. per 100 gm. per minute, and according to Stewart[6] 3.5 c.c. to 14 c.c. per 100 gm. per minute.

The slight differences from the normal heart rate and systolic pressure are not sufficient to explain the cyanosis, even in the presence of a lessened pulse pressure in Cases 1 and 2.

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[3] Lowey and Schröter: Ztschr. f. exper. Path. u. Therap., 1905, **1,** 197.

[4] Plesch: Ztschr. f. exper. Path. u. Therap., 1909, **6,** 462.

[5] Hewlett: Am. Jour. Med. Sci., 1913, **145,** 656.

[6] Stewart: Harvey Lecture, Nov. 23, 1912.

The failure to find on physical examination abnormalities sufficient to make a positive diagnosis of an abnormal circulation led us to seek for a possible change in the chemical composition of the blood. With the exception of a high hemoglobin content, the blood was normal to the ordinary tests. Spectrophotometric examination of the blood showed no alteration in the nature of the hemoglobin. The plasma was not discolored, and the available alkalinity of the blood as determined by the method of Van Slyke gave the same figure as for children of the same age.

In order to determine whether or not there was a change in the respiratory function of the lungs or tissues, which either prevent the blood from taking up oxygen in the lungs or else more completely depleted it of its supply in the tissues (either condition leading to decrease in the oxygen content of the blood), an examination of the respiratory exchange was made in Case 1 and in his control of the same age during a period of rest and the results obtained are shown in the following tabulation:

COMPARISON OF THE RESPIRATORY EXCHANGE OF THE BOY IN CASE 1 AND HIS CONTROL (NORMAL)

	Weight, Kg.	Expired air at 760 Mm. Hg. and OC., C.c.	%CO_2	CO_2 per Minute, C.c.	CO_2 per Kg. Body Weight per Min., C.c.
Case 1	32.2	2970	2.70	80	2.43
Control (normal)	37.2	2540	3.81	96.8	2.69

These results show that the cyanotic boy inspired 20 per cent. more air per minute than the normal control. However the percentage of carbon dioxid in the expired air was about 25 per cent. less, thus making the total carbon dioxid excreted per minute, when reduced to cubic centimeter excreted per kilogram body weight, practically the same in both boys. These results definitely show that the abnormality is not metabolic, and that it lies in a deficient aeration of the blood which is sent into the systemic circulation.

In the hopes that figures might be obtained which would throw light on the condition, the following experiments were made, the object of which was to determine the difference in the amount of carbon dioxid found in the arterial and the venous blood in the case of the cyanotic and the normal boy. In order to determine the change which the blood undergoes in the lesser circulation, it was necessary to compare the blood from the right with that from the left side of the heart, an operation which was practically impossible. It was therefore necessary to find other methods for estimating the amount of carbon dioxid in the venous blood. This is possible, as has been shown by Christiansen, Douglas and Haldane,[7] who have devised a method for obtaining the tension of the carbon dioxid in the venous blood. Their method consists in having the patient inspire and expire air from a spirometer, this air containing known percentage of carbon dioxid, and then estimating the carbon dioxid content of that air at the end of eight and thirteen seconds of breathing into the spirometer. As the time of the lesser circulation is somewhat greater than thirteen seconds, the air in the bag is only in contact with venous blood. Repeated tests were made, beginning with air containing approximately the amount of carbon dioxid contained in alveolar air, and again with air containing about 2 per cent. more than alveolar air. When, after repeating the test with the different percentages of carbon dioxid in the rubber bag, the point is reached at which no change takes place in the percentage composition of the test air between the eighth and the thirteenth second of breathing, the tension of carbon dioxid in the spirometer at this point equals the tension of the carbon dioxid in the venous blood. The tension of carbon dioxid in the arterial blood is that found by obtaining the percentage of carbon dioxid in the alveolar air, which is estimated by the method of Haldane.[8] This consists in estimating the percentage of carbon dioxid in the last portion of the expired air of a forcible expiration, and then determining the partial pressure of the gas at the barometric pressure and temperature at which the analysis was made. [Per cent. of carbon dioxid × (barometric pressure — vapor tensions at temperature of analysis = tension of carbon dioxid in the blood.]

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[7] Christiansen, J., Douglas, C. G., and Haldane, J. S.: Carbon Dioxid in the Blood, Jour. Physiol., 1914, **48,** 244.

Correcting the difference in the tensions between arterial and venous bloods on the basis of the influence which the oxygen concentration has on carbon dioxid tension[7] and then consulting the absorption curve of blood at the tensions of the arterial carbon dioxid and the corrected tension of venous carbon dioxid, the amount of carbon dioxid which each holds is read off. From the difference in the amount of carbon dioxid held in the arterial and in the venous blood thus determined, the amount of carbon dioxid each cubic centimeter of blood loses on passing through the lungs may be calculated. A tabulation of the results of these experiments is shown in Table 2.

Knowing the number of cubic centimeters of carbon dioxid excreted per minute and the amount of carbon dioxid in a definite amount of blood passing through the lungs, we can determine by calculation the number of cubic centimeters of blood passing through the lungs per unit of time, this latter being illustrated by quoting the following experiment made on our boys:

In Case 1 the alveolar carbon dioxid tension (Table 2) was about 35.1 mm. of mercury and the venous carbon dioxid tension was 48.9

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[8] Haldane: Method of Air Analysis, London, 1912.

mm. of mercury. This gives a difference of 13.8 mm. of mercury pressure of carbon dioxid between venous and arterial blood. In the case of the normal control boy the alveolar carbon dioxid was 39.6 mm. and the venous carbon dioxid was 45.4. This gives a difference of 5.8 mm. of mercury pressure of carbon dioxid between venous and arterial blood, the latter being the average normal figures as shown by Christiansen, Douglas and Haldane,[9] who give from 6.3 to 6.9 for adults. In other words, the difference between the tension of carbon dioxid in arterial and in venous blood is 170 per cent. greater in Case 1 than in the normal control. In Case 2 the difference is only 21 per cent. between the patient and the normal control, who unfortunately gave a difference between arterial and venous carbon dioxid tension a little greater than one would expect in a normal case, probably because of our inability to obtain a fair sample of alveolar air from him.

TABLE 2.—VARIATION IN CARBON DIOXID PRESSURE IN EQUILIBRIUM WITH THE BLOOD ENTERING AND LEAVING THE LUNGS (VENOUS AND ARTERIAL BLOOD) IN THE CASE OF THE NORMAL AND CYANOTIC BOYS

	Age, Years	Weight, Kg.	Date	Mm. Hg CO_2 Pressure		Difference Mm. Hg	Average Difference, Mm. Hg	Per Cent. Diff.
				Arterial Blood	Venous Blood			
Case 1	11	32.3	5/27	35.1	48.9	13.8		
			5/31	34.5	48.1	13.6		
			6/ 1	36	—	—		
			6/ 3	35.5	47.6	14.1	13.8	
Control (normal)	11	37.2	5/27	39.08	45.4	6.32		
			6/ 1	39.6	45.6	6	....	170
			6/ 3	39.1	44.1	5.1	5.8	
Case 2	9	23.2	6/ 1	33.4	42.3	8.9		
			6/ 3	31.8	40.2	8.4	8.7	
Control (normal)	10½	22.7	6/ 1	32.4	39.1	6.7		
			6/ 3	32.3	40	7.7	7.2	21

On reducing these figures into cubic centimeters of blood flowing through the lungs per minute or per heart beat the difference is unexpectedly great (Table 3).

The normal boy has a ventricular output of 38.4 c.c. per heart beat, which is about what we would expect from the available data of other observers, whereas in Case 1 the boy has only 13.9 c.c. per heart beat passing through his lungs. But each 100 c.c. of blood of the boy in Case 1 loses about 7 c.c. of carbon dioxid in comparison to 3 c.c. lost by 100 c.c. in the normal control's blood passing through the lungs. In other words, the effect of the reduced blood flow through the lungs in the case of the cyanotic boys is compensated somewhat by its carrying an increased load of carbon dioxid per cubic centimeter, which the blood brings up to the lungs and also by the increased amount of oxygen which the blood carries per cubic centimeter to the heart, in virtue of its increased hemoglobin contents.

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[9] Christiansen, J., Douglas, C. G., and Haldane, J. S.: Carbon Dioxid in the Blood, Jour. Physiol., 1914, **48,** 268.

The results of these analyses show that the cyanosis is not a faulty gas exchange of the blood as it passes through the lungs, for this is above normal, but rather lies in a reduction of the amount of blood which reaches the left ventricle from the pulmonary circulation. The rate of blood flow is normal or above normal through the systemic circulation. We are therefore forced to believe that the blood sent from the left ventricle is a mixture of venous and arterial blood, and that the tension of oxygen in the arterial blood is below that normally found. The larger percentage of reduced hemoglobin in their arterial blood than is found in normal individuals imparts the blue color to their skin. The amount of oxygen, however, delivered to the tissues is sufficient to meet their needs, due at least in part to the increased hemoglobin content of the blood; and the amount of carbon dioxid excreted by their lungs is kept within normal limits by the greater difference in the effectual diffusion pressure of carbon dioxid between arterial and venous blood in the lungs.

TABLE 3.—RELATIVE AMOUNT OF BLOOD FLOWING INTO THE LUNGS AT EACH HEART BEAT, AS COMPUTED FROM AVAILABLE DATA

	Albert (Blue)	Bert (Normal)
Cc. CO_2 contained in 100 c.c. of blood at average mm. Hg. pressure in arterial blood	50.5	53
C.c. CO_2 contained in 100 c.c. of blood at average mm. Hg. CO_2 pressure in venous blood.	57.5	56
C.c. CO_2 lost by 100 c.c. of blood in passing through the lungs	7	3
C.c. CO_2 excreted per minute	80	96.8
Blood flow per minute through lungs	1140 c.c.	3230 c.c.
Pulse rate	82	80
C.c. blood delivered into lungs at each heart beat	13.9	40.4

The cyanotic boys are not different from other boys in their ability to do the ordinary things of life. However, their power of endurance does not compare with that of a normal boy. When forced pulmonary ventilation is pushed, the color markedly improves. Albert can hold his breath as long as a normal boy, but he cannot stand the muscular exertion that a normal boy can. These boys are all subject to bronchitis and this tendency might be explained on the assumption that a deficient oxygen supply in the blood of the bronchial artery is a factor in producing congestion or edema in the lungs, as suggested by Martin Fisher.[10]

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[10] Fisher, Martin: Edema, John Wiley & Sons, New York, 1910.

We are led, therefore, to conclude that the pathology consists of a cardiac abnormality, basing our conclusions on the result of our studies of the respiratory exchange and corroborated by the clinical studies, as shown by the electrocardiograms and radiograms.

The methods, as outlined here, afford a new means of investigating the relationship of the pulmonic circulation to the systemic circulation, and in the present case renders the diagnosis of a septal or ductus defect highly probable.

This work is being carried on at present in the laboratory of physiology in the University of Illinois, and the laboratory of pathology of the Cook County Hospital.

We desire to extend our thanks to Drs. C. S. Williamson, F. G. Harris, W. H. Welker, A. J. Carlson, J. G. Friedman, James B. Herrick and E. S. Moore for their assistance and encouragement in this work.

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THE PHENOL EXCRETION IN THE URINE OF INFANTS, INCLUDING THE NEW-BORN *

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Phenol was first found in normal urine by von Städeler[1] in 1851. Since his day the phenols isolated from urine are phenol, paracresol, orthrocresol, pyrocatechin, hydroquinone, and para-oxybenzoic acid. The most important of these, according to Baumann,[2] Mooser,[3] and Siegfried and Zimmermann,[4] is paracresol.

Städeler tested the urine distillate qualitatively with Millon's reagent. Baumann used a gravimetric method in which he converted the phenol into crystals of tribromphenol. The first volumetric method was originated by Messinger and Vortman. This was modified by Kossler and Penny,[5] and later by Neuberg,[6] Mooser,[3] Siegfried and Zimmerman,[7] and finally by Ellinger and Henzel.[8] Among the colorimetric methods worthy of notice are those of Bananni,[9] Bordas and Bobin,[9] and Kiesel.[9] It remained, however, for Folin and Denis to devise a method which was both accurate and clinically applicable.

In 1879 H. Senator,[10] using a qualitative test for phenol, found volatile (*flüchtige*) traces of it in the urines of two infants. Three others gave negative results. Ludwig F. Meyer[11] in 1905, using the

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[1] Von Städeler, G.: Ann. d. Chem. u. Pharm., 1851, **77,** 17; cited from Baumann, E.: Ueber Gepaarte Schwefelsaüren im Organismus, Arch. f. Physiol., 1876, **13,** 287.

[2] Baumann, E.: Ueber den Nachweis und die Darstellung von Phenolen und Oxysäuren aus dem Harn, Ztschr. f. physiol. Chem., 1882, **6,** 183.

[3] Mooser, W.: Beitrag zur Kenntnis der aromatishchen Körper des Harns, Ztschr. f. physiol. Chem., 1909, **63,** 155.

[4] Siegfried, M., and Zimmerman, R.: Die getrennte Bestimmung von Phenol and Parakresol im Harns, Biochem. Ztschr., 1911, **34,** 462.

[5] Kossler, A. V., and Penny, E.: Ueber die massanalytische Bestimmung der Phenols im Harn, Ztschr. f. physiol. Chem., 1893, **17,** 117.

[6] Neuberg, C.: Ueber die quantitative Bestimmung des Phenols im Harn, Ztschr. f. physiol. Chem., 1899, **27,** 123.

[7] Neubauer and Huppert: Analyse des Harns, 1913, **2,** 788.

[8] Hensel, Marie: Zur Methodik der Phenolbestimmung im Harn, Ztschr. f. physiol. Chem., 1912, **78,** 373.

[9] Neubauer and Huppert: Analyse des Harns, 1913, **2,** 793.

[10] Senator, H.: Ueber das Vorkommen von Produktion der Darmfaulniss bei Neugeborenen, Ztschr. f. physiol. Chem., 1880, **4,** 1.

[11] Meyer, Ludwig F.: Zur Kenntnis der Phenolausscheidung beim Zäugling, Monatsch. f. Kinderh., 1905, **4,** 344.

method of Kossler and Penny, investigated the phenol excretion of seven infants and found it present in every case.

At the instigation of Dr. Otto Folin a study of the urinary excretion of phenol in normal infants was undertaken. Later, in reviewing the literature, it was found that there were no data relative to quantitative determinations on the phenol excreted by the new-born. Dr. J. P. Sedgwick, therefore, suggested that the new-born be included in this investigation.

The Folin and Denis[12] method was used with a slight modification which insures more uniform results in cold weather and gives the maximum blue color in a shorter time. In transferring the solutions to be tested for total phenol from the large test tubes to volumetric flasks, as Folin directs, the amounts of rinse water used often varied, hence the amounts of lukewarm water required in filling to volume varied accordingly. Consequently some flasks would be cooler than others. A cool flask often did not reach its maximum color for an hour or more. In this, as in most other colorimetric work, uniformity in temperature is essential to uniformity in depth of color. To avoid delay the technic was modified as follows: all flasks, after being filled to volume, were placed in a water-bath with a temperature of from 40 to 45 C. In about ten minutes all were ready for the colorimeter.

In measuring 20 c.c. of the second filtrate to be used in testing for free and for total phenol, the same pipet was used for both to insure equal volumes. Both the free and the total phenol of each specimen were read against the same standard.

In using the large test tubes placed within a tall 600 c.c. beaker, as Folin and Denis direct, it was found more satisfactory to use a wire gauze so arranged in the beaker as to support the test tubes about 3 cm. from the bottom. The top of each test tube then extends over the side of the beaker, and assisted by the contained funnel, it becomes a perfect condenser, provided the water is not boiled too vigorously. Instead of heating the test tubes over a free flame, it was found preferable to place them directly into the boiling water-bath for one minute. After this a microburner was used and the water kept hot, but not boiling, for ten minutes.

In testing known solutions of phenol, the results with a funnel condenser were compared with those obtained with a reflux condenser. When used as described above, the funnel condenser is absolutely accurate, that is, no phenol is lost by evaporation.

Folin and Denis found some cases in which the free phenol constituted 100 per cent. of the total phenol. In our cases, with the technic as described above, some combined phenol was always present. Also our average percentage of combined phenol was greater than theirs.

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[12] Folin, O., and Denis, W.: A Colorimetric Method for the Determination of Phenols (and Phenol Derivatives) in Urine, Jour. Biol. Chem., 1915, **22,** 305.

The specific gravity of infants' urine is usually 1.005 to 1.010. With such dilute urine, 20 to 25 c.c. are necessary for a test and 40 c.c. of the first filtrate are most convenient. The specific gravity of the urine of the new-born is from 1.020 to 1.030. With them 5 c.c. give the most satisfactory results and only 25 c.c. of the first filtrate are necessary.

The number of infants whose urine was studied was fifteen. With several, the urine was tested daily for three successive weeks, during which time week-end rest periods of three days each were allowed. A total of ninety-five twenty-four hour specimens were examined. The number of new-born infants whose urine was studied was nineteen. Each specimen included the urine passed during the first three days of life. In studying these 114 specimens a total of 164 analyses were made. Where two or more analyses were made on the same specimen the average only is given.

Table 1 gives the principal points needed for a metabolic study of these fifteen infants, including age, weight, sex, clinical condition, amount and kind of diet, number and consistence of stools and, in addition, the urinary record. None of these cases had hyperpyrexia at any time and the records of temperature were therefore omitted.

The diets in numbers from 4 to 12, inclusive, were prepared in the Walker-Gordon laboratory in Boston. In those cases in which homogenized milk was given the proportions of the food elements were estimated with great accuracy.

The results from the homogenizing of whole milk or of olive oil mixed with fat-free milk show no effect on the phenol excretion. This was to be expected, since it has long been established that phenols arise from proteins.

The ages of these infants varied from 1 week to 6 months, their weights varied from 1,765 gm. to 5,740 gm., the food intake from 405 to 1,080 gm. and the number of stools per day from one to nine.

The total phenol excretion per day ranged from 9 mg. in Case 14 to 58 mg. in Case 4. The average phenol excretion per day was 28.9 mg., of which 83 per cent. was free phenol.

The consistence of the stools in these cases was apparently not a determining factor in the amount of phenol excreted. This agrees with observations of Meyer[11] and with the statement of Freund[13] with reference to the output of ethereal sulphates.

For the sake of ready comparison, I have tabulated the data given by Meyer on his cases and present it in Table 2. In these cases the

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[13] Freund, W.: Zur Kenntniss der Schwefelausscheidung bei Säuglingen. Ztschr. f. physiol. Chem., 1900, **29,** 5, 24.

TABLE 1.—URINARY RECORD AND OTHER—

No.	Name	Sex	Age	Clinical Condition	Weight with Gain or Loss for Week, Gm.	Diet			
						Amount and Kind	Per Cent. Fat	Per Cent. Carbohyd.	Per Cent. Protein
4	Lamachia..	♂	3 mo.	Under nourished...	4,300	1,050 c.c. modified milk..	2.5	6	1.25
						Average..............	...	...	....
5	Casey......	♂	6 mo.	Healthy...........	3,550	1,050 c.c. modified milk..	1	5.6	1.5
						Average..............	...	...	....
6	Walsh......	♂	6 mo.	Healthy...........	5,340	1,050 c.c. modified milk..	2	6	1.75
					—60	Average for week.....	...	...	....
					5,260	1,050 c.c. modified milk.. homogenized	2	6	1.75
					No change	Average for week.....	...	...	....
					5,260	1,050 c.c. special homogenized [the 2 % fat is olive oil]	2	6	1.75
					—180	Average for week.....	...	...	....
						Avg. 22 determinations.	...	...	....

—DATA OF THE AUTHOR'S FIFTEEN CASES

Stools		Urine						
					Phenol			
Number	Form	Volume, C.c.	Specific Gravity	Total Nitrogen, Gm.	Free, Mg.	Total, Mg.	Free, per Cent.	Conjugated, per Cent.
...	....	780	.....	2.36	54.2	61.5	88	12
		630	.....	3.42	43.1	54.6	79	21
...	....	705	.....	2.89	48.6	58	83	17
...	....	750	.....	1.16	40.4	42.6	94	6
		600	.....	1.01	39.6	43.3	91	9
		930	.....	1.62	72.7	80.6	90	10
...	....	726	.....	1.26	50.9	55.8	91	9
3	△	855	.....	....	29.2	35.3	80	20
1	△	780	.....	....	25.7	31.2	80	20
1	△	840	.....	....	34.8	36.2	96	4
3	○	720	.....	....	25.6	30.6	83	17
3	○	780	.....	....	34.4	40.9	84	16
2	△	740	.....	....	37.1	39.6	93	7
1	△	825	.....	....	28.4	39.3	72	28
2	....	790	.....	2.191	30.6	35.6	86	14
3	—	780	1.008	1.394	21.6	26.2	83	17
4	△	810	1.010	1.11	23.4	27.4	86	14
2	△	750	1.009	1.471	30.6	33.3	92	8
3	△	810	1.007	2.002	27.6	32.9	80	20
		810	1.008	1.929	31.6	34.9	90	10
5	△	660	1.011	1.788	21.4	30	70	30
3	△	705	1.009	1.659	28.6	32.3	88	12
2	△	780	1.005	1.954	24.8	32.5	66	34
3	....	763	1.007	1.65	26.2	31.2	84	16
2	△	870	1.011	2.179	30.2	39.9	76	24
2	△	750	1.011	1.488	27.9	32.3	86	14
1	△	840	1.012	1.835	17.9	22	81	19
1	—	810	1.008	1.053	17	25.3	67	33
1	△	840	1.006	2.151	19.5	29	67	33
1	△	840	1.012	2.141	19.7	29.6	67	33
1	△	780	1.012	1.945	15.4	24.7	62	38
1.3	....	790	1.010	1.912	20.7	29.1	65	35
2	....	781	.....	1.917	25.8	30.9	83	17

TABLE 1.—URINARY RECORD AND OTHER DATA—

No.	Name	Sex	Age	Clinical Condition	Weight, with Gain or Loss for Week, Gm.	Diet			
						Amount and Kind	Per Cent. Fat	Per Cent. Carbohyd.	Per Cent. Protein
7	Reddish....	♀	2 mo.	Normal............	3,095	630 c.c. breast milk....	4	7	1.5
					+270	Average for week.....	...	...	....
					3,265	630 c.c. breast milk; homogenized	4	7	1.5
					+90	Average for week.....	...	...	....
					3,350	630 c.c. breast milk....	4	7	1.5
					+30	Average for week.....	...	...	....
						Avg. 19 determinations.	...	...	....
8	Zuealla.....	♂	4 mo.	Balance disturbance	3,265	945 c.c. special homogenized	1.6	6	1.28
						[Olive oil 1.6 %]			
					—90	Average for week.....	...	...	....
					3,890	945 c.c. modified milk..	1.6	6	1.28
					—120	Average for week.....	...	...	....
					3,835	945 c.c. modified milk; homogenized	1.6	6	1.28
					+30	Average for week.....	...	...	....
						Avg. 11 determinations.	...	...	....

—of the Author's Fifteen Cases—(*Continued*)

Stools		Urine						
					Phenol			
Number	Form	Volume, C.c.	Specific Gravity	Total Nitrogen, Gm.	Free, Mg.	Total, Mg.	Free, per Cent.	Conjugated, per Cent.
...	△	480	1.004	0.318	10	13.2	75	25
	△	480	1.004	0.586	9.6	11.2	85	15
8	—	465	1.005	0.895	15	17.6	85	15
5	—	465	1.006	0.65	8.1	15.3	53	47
4	—	465	.....	0.706	9.3	11	84	16
6	—	420	.....	0.513	8.4	12	70	30
5	—	480	1.010	0.524	9.2	11.4	80	20
6	—	450	1.010	0.575	9	11.8	76	24
2	—	420	.....	0.501	10	11.8	85	15
5.1	....	458	1.006	0.585	9.8	12.8	76	23
8	△	390	1.008	0.459	10.3	12.5	80	20
4	—	420	1.008	0.513	15.2	17	89	11
2	—	330	.....	0.4	7.9	12.1	65	35
5	—	360	.....	0.437	8.3	10.4	80	20
3	—	420	.....	0.464	9.6	13.9	79	21
3	—	390	.....	0.387	8.1	11	74	26
4.2	....	385	1.008	0.285	10.1	12.8	79	21
5	—	420	1.008	0.518	12.2	15.7	78	22
6	△	300	.....	0.195	7.6	10.1	75	25
3	△	360	1.006	0.464	8.8	12.3	78	22
2	—	390	1.006	0.453	7.5	9.9	75	25
4	....	417	1.007	0.407	9	12	75	25
5+	....	420	.....	0.426	9.7	12.6	77	23
2	—	780	1.010	1.355	19	23.9	80	20
6	—	840	1.008	1.083	24.3	32.8	74	26
4	△	840	1.010	1.072	22.2	31.9	70	30
4	....	820	1.009	1.17	21.8	29.5	74	26
3	○	810	1.010	1.593	35.8	47.2	78	22
1	△	600	1.012	1.239	26.6	36.1	73	27
2	○	720	1.008	1.481	35.2	42.2	83	17
2	....	710	1.007	1.437	32.5	41.8	78	22
6	—	630	1.012	1.471	21.9	23.9	90	10
9	—	390	.....	.....	17.4	20	87	13
6	—	570	1.010	1.257	17	24.2	70	30
4	△	600	1.010	1.244	12.1	17.4	69	31
2	△	630	1.011	1.339	13.3	25.9	55	45
5.5	....	560	1.010	1.303	16.3	22.3	77	23
4	....	698	1.009	1.303	23.5	31.2	76	23

TABLE 1.—URINARY RECORD AND OTHER DATA—

No.	Name	Sex	Age	Clinical Condition	Weight, with Gain or Loss for Week, Gm.	Diet			
						Amount and Kind	Per Cent. Fat	Per Cent. Carbohyd.	Per Cent. Protein
9	Adams.....	♀	4 mo.	Normal...........	4,290	960 c.c. special homogenized [Olive oil 2%; barley starch 0.75%]	2	6	1.6
					+60	Average for week.....	...	...	....
					4,430	960 c.c. modified milk.. [Barley starch 0.75%]	2	6	1.6
					+120	Average for week.....	...	...	....
					4,430	960 c.c. modified milk.. [Barley starch 0.75%]	2	6	1.6
					+60	Average for week.....	...	...	....
						Avg. 11 determinations.	...	...	....
10	Caples.....	♂	6 mo.	Acute intestinal	5,340	1,080 c.c. modified milk.. [Barley starch 0.75%]	2	6	1.75
					No change	Average..............	...	...	....
11	Gilman.....	♂	5 wk.	Malnutrition.......	1,765	750 c.c. breast milk, 8 parts; whey, 2 parts; lactose to 6%	3.2	6	1.4
					+90	Average..............	...	...	....
12	Crowley....	♂	2 mo.	"Colic"; well nourished	4,680	735 c.c. modified milk.. [Barley starch 0.75%]	2.4	6	1.9
					+90	Average for week.....	...	...	....

—OF THE AUTHOR'S FIFTEEN CASES—(*Continued*)

Stools		Urine						
					Phenol			
Number	Form	Volume, C.c.	Specific Gravity	Total Nitrogen, Gm.	Free, Mg.	Total, Mg.	Free, per Cent.	Conjugated, per Cent.
4	—	750	1.010	1.414	32.3	40.4	80	20
2	△	720	1.012	1.415	32.2	37.2	86	14
4	△	750	1.010	1.618	34.2	39.8	86	14
3.3	....	740	1.010	1.482	32.9	39.1	84	16
7	△	510	1.009	1.484	22.9	26.6	86	14
8	—	600	1.010	1.999	28.2	31.3	90	10
4	—	375	1.012	1.187	18.7	23.5	79	21
6.3	....	495	1.010	1.557	23.3	27.1	86	14
6	—	570	.....	1.482	28.5	31	92	8
4	—	510	.....	1.532	17.5	20.4	86	14
1	—	570	.....	1.48	15.5	18.7	83	17
4	△	615	1.010	1.547	16	25.6	62	38
3	△	630	1.012	1.663	26.3	29.2	83	17
3.6	....	579	1.011	1.541	20.7	24.9	84	16
4.3	....	605	1.010	1.526	25.6	30.3	85	15
6	—	780	1.010	1.171	16.6	25.1	66	34
8	△	840	.....	1.864	18.4	26.6	69	31
9	—	720	1.010	1.501	14.3	20	72	28
5	—	855	.....	1.557	21.1	24.3	87	13
7	....	799	1.010	1.523	17.6	24	73	27
8	—	420	1.004	0.198	7	9	67	33
5	—	450	1.005	0.26	8.7	11.4	76	24
10	—	570	1.005	0.279	8.9	10.6	84	16
4	—	420	1.008	0.391	10.8	11.2	96	4
7	....	465	1.006	0.382	8.8	10.5	83	17
2	△	450	1.010	1.236	19.5	24.2	80	20
3	△	690	1.012	2.019	22.5	30	75	25
3	△	660	1.010	1.926	13.8	20.1	68	32
4	△	690	1.014	2.618	13.5	16.4	80	20
3	....	622	1.011	1.975	17.3	22.7	77	23

TABLE 1.—Urinary Record and Other Data—

No.	Name	Sex	Age	Clinical Condition	Weight, with Gain or Loss for Week, Gm.	Diet			
						Amount and Kind	Per Cent. Fat	Per Cent. Carbohyd.	Per Cent. Protein
12 Cont.	Crowley....	♂	2 mo.	"Colic"; well nourished	4,770	735 c.c. special homogenized [Olive oil 2.4%; barley starch 0.30%]	2.4	6	1.9
					—60	Average for week.....	...	...	....
						Avg. 9 determinations..	...	...	....
13	Glover....	♂	2 wk.	Normal...........	2,860	Breast fed, 5 feedings...	...	...	....
						[Amount not recorded]			
					+40	Average for week.....	...	...	....
14*	Vincent....	♂	1 wk.	Normal...........	2,860	Breast fed, 5 feedings...	...	...	....
						[Amount not recorded]			
					+80	Average for week.....	...	...	....
18	Packer.....	♂	3 mo.	Normal; undernourished	3,600	750 c.c. protein milk + 7% dextrimaltose	...	...	....
					+120	Average for week.....	...	...	....
20	Tollefson..	♂	6 mo.	Cleft palate; otitis media	4,950	750 c.c. ½ milk, ½ oatmeal water + 4% sugar; cereal b.i.d.	...	...	....
					—50	Average for week.....	...	...	....
21	Samuelson	..	6 wk.	Healthy...........	5,740	960 gm. breast milk.....	...	...	....
					+210	Average for week.....	...	...	....
22	Voulas....	..	9 wk.	Healthy...........	2,840 —70	405 gm. breast milk.....	...	...	....
						General average of the 15 cases............			

* A 72-hour specimen.

—OF THE AUTHOR'S FIFTEEN CASES—(*Continued*)

Stools		Urine						
					Phenol			
Number	Form	Volume, C.c.	Specific Gravity	Total Nitrogen, Gm.	Free, Mg.	Total, Mg.	Free, per Cent.	Conjugated, per Cent.
4	△	525	.....	1.162	14.9	17.3	85	15
4	△	630	1.012	1.741	18.8	19.2	97	3
4	△	600	1.010	1.578	....	25.9	..	..
3	△	480	1.012	1.334	13.3	20	66	34
4	—	480	1.014	1.465	14.3	23	67	33
4	....	543	1.012	1.465	15.3	21.1	73	27
3.5	....	583	1.011	1.686	16.3	21.9	75	25
1	△	120	1.006	0.265	8.6	11.1	77	23
1	△	180	.....	0.264	15.6	16.1	97	3
...	....	150	1.006	0.264	12.1	13.6	89	11
2	△	...	.....	.....	....	....	..	..
1	△	...	.....	.....	....	....	..	..
1	△	100	1.022	0.88	22.6	27.1	83	17
...	....	34	.....	0.293	7.5	9	83	17
1	□	250	1.012	1.1	14.9	17.3	87	13
2	△	200	1.008	1.27	15.3	16.7	92	8
...	....	225	1.010	1.185	15.1	17	89	11
1	△	240	1.010	0.947	24	27.5	87	13
1	△	180	1.014	1.436	37.7	40.1	94	6
...	....	210	1.012	1.192	30.8	33.8	91	9
2	△	425	1.010	0.509	28.7	38.3	75	25
2	△	380	1.006	0.316	28.4	35.2	81	19
...	....	402	.....	0.412	28.5	36.7	78	22
2	○	155	1.007	0.358	18.6	21.6	87	13
...	....	463	.....	1.107	24	28.9	83	17

Characters indicating consistency of stools are as follows: ○, formed; △, intermediate or soft; —, watery; □, soap stool.

phenol excretion varies from 2.5 to 16.9 mg., the average for his breast-fed infants being 4.19 mg. and for the artificially fed infants 13.28 mg. He does not state the daily output of urine or the total nitrogen. These figures of Meyer constitute the only quantitative investigations made on infants previous to 1915 found in a thorough review of the literature.

TABLE 2.—Data Derived from L. F. Meyer's Cases

No.	Age	Weight, Gm.	Clinical Condition	Diet	Stools	Phenol, Mg.
1	6 mo.	6,330	Healthy..............	850 gm. breast milk	....	5.87
2	10 wk.	.....	Healthy..............	600 gm. breast milk*	....	2.507
3	7 wk.	3,450	Healthy..............	Condensed milk "Schleim" and sugar	3 yellow, thin	8.46
4	5¾ mo.	4,350	Healthy..............	Solution of powdered milk	3 yellow, thin	12.22
5	13 mo.	5,740	Very rachitic.........	600 gm., ½ milk, ½ flour and gruel soup	3 yellow, thin	13.16
6	4¼ mo.	4,000	....	½ flour soup, ½ powdered milk solution	4 yellow, thin	15.67
7	10 mo.	5,020	Underdeveloped, rachitic, perspiring greatly	Breast milk and buttermilk†	1 yellow, homogeneous	16.92

* Average in breast-fed infants 4.19.
† Average in artificially-fed infants 13.28.

TABLE 3.—Phenol Excretion in Urine of Hospital Infants (Folin and Denis)

No.	Age, Mo.	Clinical Condition	Volume, C.c.	Total N, Gm.	Phenol			
					Free, Mg.	Total, Mg.	Free, per Cent.	Conjugated, per Cent.
61	10	Malnutrition.....	860	1.3	42	43	98	2
63	4	Malnutrition.....	740	1.8	40	40	100	0
64	2	Malnutrition.....	550	1.6	68	68	100	0
65	2	Malnutrition.....	610	1.7	31	35	89	11
71	6	Malnutrition.....	755	1.5	40	42	95	5
60	3	Normal...........	600	1.3	30	50	70	30
66	10	Rachitic..........	620	2.9	50	60	77	23
Aver.	5.3	....	695	1.74	43	48	89	11

Folin and Denis,[14] in reporting results by their method, mention seven infants whose phenol excretion averages 48 mg., as shown in Table 3.

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[14] Folin, O., and Denis, W.: The Excretion of Free and Conjugated Phenols and Phenol Derivatives, Jour. Biol. Chem., 1915, **22,** 309.

The weight of these infants is not mentioned, nor is the number or character of their stools. The amount and character of diet is also omitted. However, the comparatively large excretion of urine, total nitrogen, and phenol would indicate, as compared with our cases, that these infants were given artificial food.

A rather striking fact is found in Cases 63 and 64, in that the free phenol equals the total phenol. Whether these results were verified by other tests on these specimens is not stated. In the cases included in this investigation it was found several times that the amount of free phenol equaled or exceeded the total phenol. However, carefully repeated experiments on these same specimens showed that the error was due to the loss of phenol by evaporation during heating.

Nevertheless, Folin and Denis' general average of 89 per cent. of free phenol and ours of 83 per cent. show what a remarkably large percentage of the phenol is excreted in the free form; this, too, in spite of the fact that the latest text books on biochemistry (Hammarsten, Matthews, Hawk, and Neubauer and Huppert), so far as they refer to this point at all, state the opposite.

To show that the number of stools per day has an effect on the excretion of phenol, as Folin believed and as Salkowski,[15] Brieger,[16] Russo,[17] and Strasser[18] have shown, we have gone over the clinical charts available on our cases and tabulated the findings in Table 4.

If one considers three stools per day to be normal for infants, then of the twenty-two comparisons here shown, ten are normal and twelve are abnormal. The average excretion of phenol by those having three stools per day or less is 26.1 mg., and for those having over three stools per day the average is 21.7 mg. If, however, one compares those having four or more stools with those having three or fewer, the results are more striking. The average phenol excretion of those having three stools or less per day is 26.1 mg. but for those having four stools or more per day the average is 16.2 mg.

A comparison of Cases 10 and 20, two children of the same age, whose total nitrogen excretions were 1.5 and 1.2 gm., respectively, and whose phenol excretions were 24 and 34 mg., apparently furnishes a striking example of the effect of diarrhea on phenol excretion. Whether this is due entirely to the enteral or to parenteral metabolism can hardly be considered a settled question.

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[15] Salkowski, E.: Verschliessung des Darmkanals auf die Bildung der Karbolsäure im Körper, Berl. deutsch. Gesellsch., 1876, **9**, 1595; ibid., 1877, **10**, 842.

[16] Brieger, L.: Ueber Phenolausscheidung bei Krankheiten and nach Tyrosinbebrauch, Ztschr. f. physiol. Chem., 1878, **2**, 241; Zur Kenntniss der Fäulnissalkaloids, Ztschr. f. physiol. Chem., 1882-1883, **7**, 274.

[17] Russo, A.: Sulla eliminazione del fenolo delle urine, Revista clin. e. terap., 1888, Okt.; Abstr. Centralbl. f. klin. Med., 1889, **10**, 306.

[18] Strasser, A.: Ueber die Phenolausscheidung bei Krankheiten, Ztschr. f. klin. Med., 1894, **24**, 543.

TABLE 4.—Phenol Excretion with Reference to Number of Stools Per Day

Number	Change in Weight During Investigation, Gm.	First Week		Second Week		Third Week	
		Number of Stools	Total Phenol, Mg.	Number of Stools	Total Phenol, Mg.	Number of Stools	Total Phenol, Mg.
6	— 360	2	35.6	3.1	31.2	1.3	29.1
7	+ 295	5.1	12.8	4.2	12.8	4	12
8	+ 600	4	29.5	2	41.8	5.4	29.3
9	+ 200	3.3	39.1	6.3	27.1	3.6	24.9
10	0	7	24				
20	— 50	1	33.8				
11	+ 90	7	10.5				
12	+ 30	3	22.7	4	21.1		
13	+ 40	2	13.6				
14	+ 80	1.3	9				
18	+ 120	1.5	17				
21	+ 210	2	36.7				
28	— 70	2	21.6				

Changes in weight have no demonstrable effect.

For the purpose of a further metabolic study with reference especially to artificial and breast feeding, the more important factors are summarized in Table 5.

The artificially fed infants show a phenol excretion of 8 mg. per kilogram of body weight; breast fed, 5 mg. per kilogram. Mayer[19] does not give the weights of all his infants. Nevertheless, he observed that "the decomposition in those fed on cow's milk allowed the formation of more phenol than in those fed on breast milk."

In so limited a number of cases any proportion must be ascribed partly to accident. In our fifteen cases the artificially fed compared with the breast fed show a phenol excretion ratio of 2 to 1, in Meyer's cases 3 to 1. Unfortunately, Meyer does not give the total nitrogen excretion in his cases, so we cannot compare results with reference to the protein intake.

That age and consequent increase of protein in the diet, as evidenced by total nitrogen excretion, have a decided effect on phenol excretion is indicated in the following averages:

Age	Total N, Gm.	Total Phenol, Mg.
4 to 6 months (6 cases)............	1.454	34.3
1 to 3 months (7 cases)............	0.763	25.5

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[19] Mayer, P.: Ueber Indroxyl-, Phenol-, und Glycuronsäureausscheidung beim Phloridzindiabetes, Beitr. z. Chem. Physiol. u. Path., 1902, **2**, 217.

It is also noteworthy that, without reference to age, an increase in total nitrogen is accompanied by an increase in total phenol. From our study a working rule might be formulated: *Trebling the protein intake doubles the phenol excretion.*

TABLE 5.—A COMPARISON OF DIETS

Number	Age, Mo.	Weight, Kg.	Urine, C.c.	Total Phenol, Mg.	Total Nitrogen, Gm.
Artificial milk					
4	3	4.3	705	58	2.89
5	6	3.6	726	55.8	1.26
6	6	5.1	781	30.9	1.917
8	4	3.5	698	31.9	1.303
9	4	4.4	605	30.3	1.526
10	6	5.3	799	24.0	1.528
12	2	4.7	583	21.9	1.686
20	6	4.9	210	33.8	1.192
18	3	3.7	225	17	1.185
Average	4.1	4.4	591	33.7	1.609
Breast milk					
7	2	3.2	420	12.6	0.426
11	1.25	1.8	465	10.5	0.382
13	0.5	2.9	150	13.6	0.264
14	0.25	2.9	34	9	0.293
21	1.50	5.9	402	36.7	0.412
22	2	2.8	155	21.6	0.358
Average	1.25	3.3	271	17.3	0.356

The nitrogen-phenol ratio in adults is shown by summarizing the cases reported by Folin and Denis[14] as follows:

Diet	Total N, Gm.	Total Phenol, Gm.
High protein (14 cases)..........	18.76	0.443
Low protein (16 cases)...........	5.98	0.24

These thirty cases were from the usual run of city hospital patients, including typhoid, pernicious anemia, carcinoma, pleurisy, and three cases of pneumonia with temperatures of from 103 to 104.

They also compared high and low protein diets in the same individual on each of three cases, with the following average results:

Diet	Total N, Gm.	Total Phenol, Gm.
High protein	19.2	0.428
Low protein	6.7	0.215

TABLE 6.—Phenol Excretion of

No.	Name	Clinical Condition	Age in Hours at Start of 72 Hr. Spec.	Weight		Stools
				At Birth	Gain or Loss in 72 Hours, Gm.	
23	Lepisto........	Pemphigus..............	8	2,710	—250	2, meconium
24	Schonning.....	Normal..................	36	4,215	+ 60	2, meconium; 1, △
25	Lohn...........	Normal..................	27	3,365	— 5	2, meconium; 1, △
26	Ranta..........	Icterus, pemphigus.......	3	3,725	—585	3, meconium
27	Kester..........	Icterus..................	38	4,090	—250	1, meconium; 1, △
28	Bromberg......	Perioral dermatitis......	1	3,505	—310	2, meconium; 1, △
29	Tish............	Icterus..................	12	2,945	— 40	2, meconium
30	Hatcher........	Icterus..................	17	2,990	—225	2, meconium; 1, △
31	Strander.......	Normal..................	22	3,355	—260	2, meconium; 1, △
32	Jorgensen......	Icterus..................	0.5	3,630	—440	2, meconium
33	Anderson......	Icterus..................	1	4,115	—325	2, meconium
35	Anderson......	Icterus..................	1	3,585	—440	3, meconium
36	Moore..........	Icterus..................	0	3,690	—290	1, meconium
37	Anderson......	Normal..................	0.5	2,805	—265	2, meconium
38	Peterson.......	Normal..................	2	3,650	—310	3, meconium
39	Conklin........	Normal..................	0	3,025	.....	2, meconium
40	Rohl...........	Pale, cephalhematoma...	0.5	4,630	—250 in 48 hours	○
41	Arkell..........	Icterus..................	1	3,275	—255	3, meconium
42	Olson..........	Normal..................	2	4,215	—475	1, meconium; 1, △
Average.............		....	..	3,655	.....	....

It is to be noted that this rule—trebling the protein doubles the phenol—which was worked out on infants, applies also to adults, when considered collectively.

In comparing the results of Folin and Denis in their experiments on infants (Table 3) with the fifteen included in this investigation (Table 1) and applying the rule given above, we find an explanation for their average of 48 mg. as compared with ours of 29 mg.

$$\begin{array}{rcrcrcl} \text{Total N} & : & \text{Total N} & :: & \text{Phenol} & : & \text{Phenol} \\ 1.74 & : & 1.107 & :: & 48 & : & x\ (=30) \end{array}$$

If it be true that the excretion of nitrogen and of phenol bears a definite relation both in infancy and adult life, without reference to disease, weight, length of bowel or number of stools, may it not be

-Newborn Infants in Nineteen Cases

Temperature Range in the 72 Hours	Urine							Remarks
				Phenol				
	Volume, C.c.	Specific Gravity	Total Nitrogen, Mg.	Free, Mg.	Total, Mg.	Per Cent. Free	Per Cent. Conjugated	
98 to 100.6	48	1.022	320	7.9	10.3	76	24	
98.6 to 99.4	93	1.026	1,427	16.7	20.2	82	18	
98 to 99.2	60	1.018	400	12.8	20.6	62	38	
98.6 to 103.6	47	1.027	382	15.6	19.9	77	23	May be a 48 hr. spec. only
98.6 to 100	69	1.024	853	15.4	23.4	66	34	
98.6 to 100.4	54	1.022	481	14.1	15.1	93	7	
97.8 to 98.4	36	1.018	147	7.8	8.3	85	15	
97.4 to 99	31	1.026	157	4.3	5.1	84	16	Received 15 c.c. water 5 hrs. before spec. started
98.2 to 99.2	55	1.024	610	12.1	13.4	90	10	Received 15 c.c. water 4 hrs. before spec. started
97.2 to 100.2	14	.....	94	1.2	2.9	41	59	
97.6 to 99	34	.....	275	11.8	14.6	81	19	
97.2 to 99.6	25	.....	127	7.4	8.5	87	13	
96.8 to 100	11	.....	39	1.8	2.1	86	14	
97 to 101	23	.....	198	4.6	5.7	80	20	
98 to 98.6	43	1.006	301	7.2	8.8	82	18	
96.4 to 98	33	1.011	199	4.6	6	77	23	
96.4 to 97.6	70	1.016	491	12.1	15.1	80	20	Died at 76 hrs. of subdural hemorrhage
96.2 to 100	7	.....	...	2.4	34	70	30	
96.6 to 100.8	34	1.016	280	8.6	9.9	86	14	
....	41	.....	376	8.7	11.2	76	24	

true, as claimed by Blumenthal and Lewin,[20] that the phenol in the urine is also, in part at least, a product of endogenous metabolism?

Blumenthal and Lewin found an increased phenol excretion in cachetic cancer and increased protein catabolism following phloridzin injection. Mayer[19] and Schulz[21] were unable to verify these results in animal experiments after phloridzin injection.

The findings of Mayer and Scholz were accepted as correct by A. Ellinger.[22] He also accepted the statements of Senator[10] and of

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[20] Lewin: Phenol and Indoxyl im intermed. Stoffwechselen, Beitr. z. Chem., Physiol. u. Pathol. (Hofmeister), 1902, **50,** 472; cited from Meyer, L. F.: Footnote 11.

[21] Scholz, H.: Beiträge zur Frage der Entstehung des Indicans im Tierkörper, Ztschr. f. physiol. Chem., 1903, **38,** 513.

[22] Ellinger, A.: Neubauer and Ruppert's Analyse des Harns, **2,** 766.

Schild[23] as proof that phenol is formed only through bacterial action within the bowel, Schild having demonstrated that, in the hot summer months, the bowel is sterile for an average of twelve hours after birth.

Senator[10] tested the urine, liquor amnii, and meconium, using Baumann's[24] distillation method and testing the distillate with Millon's reagent. The conjugated sulphates (phenol and cresol) he converted into tribromphenol and tribromcresol. In testing the urine he used an average of 33 c.c., which must have required from one to three days to collect. Out of five tests on the urine only two were positive. The liquor amnii and meconium were both negative, as were also the stools until the children were a month or more of age.

The question of the origin of phenol seemed therefore to rest largely on their presence or absence in the urine of the new-born.

In an attempt to answer this question, using the Folin and Denis method modified as above described, urines were collected at the University of Minnesota hospital from the new-born during the first three days of life. The infants were treated according to the usual hospital routine, being put to the breast every four hours after the first half day. Only two cases (30 and 31) received any water during the three days and those only 15 c.c. each. The specimens were collected from male babies in the winter time and were preserved with chloroform and kept on ice. Nineteen cases in all were studied, with results as given in Table 6.

Phenol was present in every case, the amounts varying from 2.1 to 23.4 mg. The average urine volume for three days was 41 c.c., the average loss of weight 260 gm. If the weight at the end of the three days be used as a basis, the excretion per kilogram is 3.4 mg. This seems remarkable when we consider that this is practically a period of starvation.

The average total phenol excretion was 11.2 mg., of which 76 per cent. was free and 24 per cent. conjugated. The total nitrogen averaged 376 mg. Furthermore, compared with infants, the phenol content and total nitrogen are both low. If we apply the nitrogen-phenol rule to these cases we find, $1.74 : 0.376 : : 48 : x$ (10.4). The computed phenol result (10.4) approximates the obtained result (11.2) closely enough to indicate that when taken collectively, the nitrogen-phenol ratio in fasting new-born infants is approximately the same as in other infants and in adults.

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[23] Schild, W.: Das Auftveten von Bacterien im Darminhalte Neuge borener vor der ersten Nährungsaufnahme, Ztschr. f. Hyg. u. Infectionskrankh., 1894, **19,** 113.

[24] Baumann, E.: Ueber gepaarte Schwefelsaüren in Organismus, Arch. f. Physiol., 1876, **13,** 285.

SUMMARY

The Folin and Denis method of determining total phenol in the urine gives more uniform results in cold weather when modified as here suggested.

An increase in the number of stools per day is associated with a decrease in the total phenol output.

In this series of fifteen infants the phenol excretion per kilogram of body weight is less in the breast-fed than in the artificially fed infant.

In infants and in adults, so far as it is possible to determine from the limited number of cases now at hand, there is an interrelation between the total phenol excretion and the protein intake as measured by the total nitrogen excreted in the urine. This relation can be expressed in the general term, *trebling the protein intake doubles the phenol excretion.*

Contrary to the earlier findings, phenol is quantitatively present in the urine of every new-born infant, the average of these nineteen cases being 11.2 mg. for the first three days of life.

As phenol is present during this period of starvation, it must originate in part through endogenous metabolism.

I am gratefully indebted to Dr. Fritz B. Talbot of the Massachusetts General Hospital, Dr. Henry I. Bowditch of the Boston Floating Hospital and Dr. J. P. Sedgwick of the University of Minnesota Hospital, for the careful collection of the urine specimens and for the clinical data on these cases.

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STUDIES IN THE CHEMISTRY OF THE SPINAL FLUID OF CHILDREN *

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Due in part to the fact that a new method for the treatment of chorea, necessitating the frequent withdrawal of spinal fluid, has been used at the hospital[1] we were fortunate enough, during the past year, to obtain for examination the spinal fluids from a rather large number of children. It appeared of interest to examine these fluids for their nonprotein nitrogenous constituents and their reducing substances, by means of the newer methods of Folin and Denis and their co-workers.

NONPROTEIN NITROGENOUS CONSTITUENTS

Up to the present, no examinations appear to have been made of the spinal fluid for its nonprotein nitrogenous constituents (total nonprotein nitrogen, urea, uric acid, and creatinin) by means of the accurate and relatively simple methods of Folin and Denis and others.[2] Woods[3] examined the spinal fluid in chronic nephritis for total nonprotein nitrogen and urea. He found that the total nonprotein nitrogen was, as a rule, 25 per cent. lower than that of the blood. The urea content of the spinal fluid approximately equaled that of the blood. Cullen and Ellis[4] found the concentration of urea in the spinal fluid the same as that in the blood. While our work was in progress, Myers and Fine[5] reported the results of their analysis of the spinal fluids from fifteen cases of nephritis in adults. Their conclusions were that the concentration of urea in spinal fluid averaged 88 per cent. of that in the blood; the concentration of creatinin averaged 46 per cent. of that in the blood; the concentration of uric acid averaged 5 per cent. of that in the blood; and the concentration of sugar averaged 57 per cent. of that in the blood.

REDUCING SUBSTANCE

Very few contributions have been made to the chemistry of the reducing substance of the spinal fluid. According to Mott,[6] Claude

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[1] Goodman, A. L.: Arch. Pediat., 1916, **31,** 649.

[2] Leopold and Bernhard: Am. Jour. Dis. Child., 1916, **11,** 432.

[3] Woods, A. C.: Arch. Int. Med., 1915, **16,** 577.

[4] Cullen and Ellis: Jour. Biol. Chem., 1915, **20,** 511.

[5] Myers and Fine: Proc. Soc. Exper. Biol. and Med., 1916, **13,** 126.

[6] Mott, F. W.: Lancet, London, 1910, **2,** 1, 79.

Bernard demonstrated the existence of sugar in the spinal fluid. Halliburton came to the conclusion that the reducing substance was not sugar, but pyrocatechin. He later abandoned that view, however, and, according to Mott, now agrees with the great majority of other observers, that the reducing substance is glucose, and that it is always present in the spinal fluid in normal conditions. Schloss and Schroeder[7] recently examined normal and pathologic spinal fluids in children for their sugar content, employing the Lewis and Benedict method. They found that the sugar content in normal fluids varied between 0.05 and 0.139 per cent. They also demonstrated that the sugar content is usually reduced in all forms of meningitis, although it may at times be normal in tuberculous meningitis. In infantile paralysis, syphilis, and idiocy the sugar content was normal. Connell[8] considers the absence of sugar in the spinal fluid a certain sign of meningitis, but its presence is no absolute proof that meningitis does not exist. The sugar content of the spinal fluid was investigated by Kopetzky[9] in eight normal cases, by means of the Benedict method; he found that it varied between 0.02 and 0.04 per cent. According to the same observer, in "the estimation of the presence of the carbohydrate body in the spinal fluid, and the determination of its absence, we have one of the earliest and most reliable signs of meningitis, and later a reliable test to afford information as to the progression or retrogression of the infection of the meninges."

PERSONAL STUDIES

We have examined the spinal fluids of fifty-nine children for nonprotein nitrogen, urea, uric acid, creatinin and sugar. The reaction of the spinal fluid was tested with litmus paper in every case. A cell count, globulin test, and Wassermann reaction were also done.[10]

METHODS

The methods employed for the nonprotein nitrogenous constituents were those of Folin and Denis and their co-workers, as described by us in a previous communication.[2] A modification of the Lewis and Benedict method was used in our sugar estimation.[11]

The results of the examination of ten normal spinal fluids withdrawn for diagnostic purposes are shown in Table 1. The nonprotein nitrogen varied between 17 and 26 mg. per 100 c.c. of fluid, the average amount being 21 mg. The urea varied between 7 and 13.5 mg. per 100 c.c. of fluid, the average amount being 9.9 mg. The creatinin varied between 0.7 and 1.5 mg. per 100 c.c. of fluid, the average amount being 0.9 mg.

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[7] Schloss and Schroeder: Am. Jour. Dis. Child., 1916, **11,** 1.

[8] Connoll: Quart. Jour. Med., 1909, **3,** 152.

[9] Kopetzky: Research Prize, Am. Laryngol., Rhinol. and Otol. Soc., Philadelphia, 1912.

[10] Done by Drs. H. Cohen, Saunders, Gordon and Fuller of the house staff of the German Hospital.

[11] Myers and Fine: Essentials of Path. Chem., 1915.

In the normal spinal fluids examined there was a slightly positive reaction present for uric acid in a few cases, but in not a single instance was there enough uric acid present to give a positive quantitative test. Myers and Fine[5] have shown that in cases of nephritis the concentration of uric acid averaged only 5 per cent. of that in the blood. According to Cushing[12] the cerebrospinal fluid is chiefly secreted by the choroid plexus. The cells of the choroid plexus are relatively impermeable to the passage from the blood stream of drugs and such substances as bile pigments, which in conditions of jaundice quickly stain all body tissues and fluids. From the results of our analysis we must conclude that uric acid, one of the constituents of the blood, does not pass readily through the choroid plexus into the spinal fluid in normal individuals.

TABLE 1.—ANALYSES OF THE SPINAL FLUID IN NORMAL CHILDREN

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction	
					Nonprotein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood
2278	F.	5	24	Alk.	26	8.5	0	0.7	0.07	6	0	0	0
2279	F.	1½	23	Alk.	19	7.5	0	0.7	0.07	3	0	0	0
2334	M.	10	51	Alk.	23	9.5	0	0.7	0.07	25	0	0	0
2461	F.	8	44	Neut.	17	8.5	0	1	0.07	3	0	0	0
2648	F.	9	50	Alk.	19	10.5	0	1.5	0.07	1	0	0	
2615	F.	9	53	Alk.	23	11.5	0	1.5	0.07	2	0	0	
3134	F.	2	19	Neut.	20	7	0	0.7	0.1	41	±	0	
3204	M.	1½	18	Alk.	20	10	0	1	0.08	6	0	0	
3940	M.	5	..	Alk.	22	12.5	0	1	0.09	..	..	0	
3978	M.	4	32	Alk.	24	13.5	0	1	0.07	3	0	0	0
Average..................................					21	9.9	0	0.9	0.07				

The sugar content of the spinal fluid was very constant, and varied between 0.07 and 0.1 per cent., the average content being 0.07 per cent. These figures correspond very closely with those given by Schloss and Schroeder,[7] and are considerably higher than those reported by Kopetzky.[9]

In Table 2 are shown the figures obtained in the analysis of the spinal fluid as compared with the blood of normal children. Our results show that in normal cases lower values for the nonprotein nitrogenous constituents are obtained in the spinal fluid than in the blood. The average concentration of the nonprotein nitrogen in the spinal fluid averaged 75 per cent. of that in the blood; the average concentration of urea in the spinal fluid averaged 82 per cent. of that in the blood; and the average concentration of creatinin in the spinal fluid averaged 60 per cent. of that in the blood.

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[12] Cushing: Jour. Med. Research, 1914, **31,** 1.

TABLE 2.—COMPARISON BETWEEN NONPROTEIN NITROGENOUS CONSTITUENTS AND SUGAR OF BLOOD AND SPINAL FLUID

	Nonprotein N, Mg. per 100 C.c.	Urea N, Mg. per 100 C.c.	Uric Acid, Mg. per 100 C.c.	Creatinin, Mg. per 100 C.c.	Sugar as Dextrose, Mg. per 100 C.c.
Blood	28	12	1.8	1.5	0.1
Spinal fluid	21	9.9	0	0.9	0.07

FLUIDS FROM DISEASED CHILDREN

The results of the analysis of the spinal fluid in twenty-one cases of chorea are given in Table 3. It is of interest to note that the figures obtained for the nonprotein nitrogenous constituents and for the reducing substances showed no variation from the normal. The cell count was above normal in only four cases. The globulin reaction was negative in every case but one, in which the result was doubtful. The Wassermann reaction of the spinal fluid was invariably negative. From the negative Wassermann reactions obtained in our cases we conclude with Morse and Floyd[13] that syphilis plays no direct part in the etiology of chorea. In one case of chorea with severe symptoms of long duration the *Streptococcus viridans* was found in the spinal fluid.

Tables 4, 5, and 6 give the results of the examination of the spinal fluid in cases of idiocy, syphilis, epilepsy, and enuresis. The findings showed no changes from the figures obtained in normal cases.

The spinal fluid was examined in two cases of acute nephritis (Table 7). One case without uremic symptoms showed a slight increase in the total nonprotein nitrogen. There was present a trace of uric acid, which was not observed in normal cases. The urea, creatinin and sugar content were normal. In one case of nephritis with uremic symptoms the total nonprotein nitrogen, urea and creatinin were markedly increased. There was present a trace of uric acid. A comparison of the figures obtained in the spinal fluid and in the blood is shown. The latter were very much higher than those obtained in the spinal fluid.

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[13] Morse and Floyd: Am. Jour. Dis. Child., 1916, **12,** 61.

We have examined the spinal fluid (Table 8) in one case of serous meningitis secondary to pneumonia, three cases of tuberculous meningitis, two cases of cerebrospinal meningitis, and one case of streptococcus viridans meningitis. In the case of serous meningitis the nonprotein nitrogenous constituents and the sugar content were within normal limits, the globulin reaction was negative, and the cell count was normal. In three cases of tuberculous meningitis the total nonprotein nitrogen and the urea were normal. The creatinin was slightly increased in two cases, and was normal in one case.

TABLE 3.—Analyses of Spinal Fluid in Chorea

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction	
					Nonprotein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood
1777	F.	8	49	Neut.	24	8.5	0	1.3	0.08	6	0	0	
1889	F.	12	55	Neut.	..	12	0	1	0.08	4	0	0	
2358	M.	8	39	Alk.	22	9	0	1	0.07	3	0	0	
2539	M.	7	41	Alk.	25	11	0	1.5	0.08	—	—	0	
2494	F.	4	35	Alk.	24	11.5	0	1.1	0.08	4	0	0	
2525	F.	5	38	Alk.	21	10	0	0.7	0.07	1	0	0	
1889	F.	12	54	Alk.	25	12.5	0	1	0.06	4	0	0	
2791	M.	6½	45	Alk.	25	10.5	0	1	0.08	3	0	0	0
2746	F.	7	50	Alk.	22	9	0	1	0.07	4	0	0	
3060	F.	8	42	Alk.	24	13	0	1	0.07	7	0	0	
2947*	M.	11	67	Alk.	20	10.5	0	1	0.06	11	0	0	0
3558	F.	13	94	Alk.	21	9.5	0	1	0.07	5	0	0	0
3060	F.	8	42	Alk.	18	9	0	1	0.07	4	0	0	0
3751	M.	7	36	Alk.	24	10.5	0	1	0.08	0	0	0	
3742	M.	8	50	Alk.	25	12	0	1	0.08	31	±	0	
3932	M.	7	50	Alk.	24	14.5	0	1	0.07	4	0	0	±
4153	F.	9	47	Alk.	19	11.5	0	1	0.06	5	0	0	0
4354	M.	6	42	Alk.	25	13.5	0	1	0.07	12	0	0	
4819	F.	10	53	Alk.	24	12.5	0	1	0.05	5	0	0	
4794	M.	11	69	Alk.	30	16	0	1	0.06	3	0	0	
3960	F.	8	52	Alk.	24	11.5	0	1	0.07	28	0	0	

Uric acid was present in every case of tuberculous meningitis. In one instance there was a trace of uric acid, and in the other two cases 0.7 and 1.2 mg., respectively, per 100 c.c. of fluid. The sugar content was normal in one case and reduced in two. The globulin reaction was invariably positive. The cell counts were much increased. In two cases of cerebrospinal meningitis, in which the meningococcus was

TABLE 4.—Analyses of Spinal Fluid in Idiocy

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Diagnosis
					Non-protein N	Urea N	Uric Acid	Creat-inin				Spinal Fluid	Blood	
1358	F.	2	25	Neut.	21	9	0	1.5	0.06	14	+	0	0	Idiocy
662	M.	1	19	Alk.	21	10.5	0	2.4	0.08	4	+	0	0	Idiocy
1775	M.	6	33	Alk.	..	11	0	1	0.08	6	+	0	0	Idiocy
2445	F.	5	28	Alk.	21	11.5	0	1	0.06	5	0	0	—	Idiocy, mongolian
2565	F.	2	22	Neut.	23	11.5	0	1	0.06	3	0	0	0	Idiocy
2680	M.	6	51	Alk.	25	10.5	0	1.5	0.07	1	0	0	0	Idiocy, mongolian
3244	M.	8	46	Alk.	21	9	0	1	0.06	4	0	0	0	Idiocy

TABLE 5.—Analyses of Spinal Fluid in Syphilis

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Diagnosis
					Non-protein N	Urea N	Uric Acid	Creat-inin				Spinal Fluid	Blood	
7961	M.	10	55	Neut.	15	5	0	1.5	0.06	4	0	0	4+	Syphilitic synovitis
815	F.	14	61	Neut.	24	13	Faint trace	0.5	0.07	4	0	0	4+	Bone syphilis
3933	F.	7	44	Alk.	21	10.5	0	1	0.07	22	0	10+	4+	Syphilis
4024	M.	11	61	Alk.	19	9.5	0	1	0.07	4	0	0	4+	Syphilis

TABLE 6.—ANALYSES OF SPINAL FLUID IN MISCELLANEOUS CASES

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Diagnosis
					Non-protein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood	
2144	F.	8	62	Alk.	24	10.5	0	0.5	0.08	4	0	0	—	Encursis
1136	M.	6	46	Neut.	25	9.5	0	1.5	0.07	40	+	—	—	Epilepsy
1611	M.	11	73	Neut.	21	12.5	0	1	0.08	5	0	0	—	Epilepsy

TABLE 7.—ANALYSES OF SPINAL FLUID IN ACUTE NEPHRITIS

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Remarks
					Non-protein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood	
2208	F.	7	38	Alk.	33	13	Trace	0.8	0.08	8	0	0	—	Albumin in urine with many hyaline and granular casts; few coarse granular casts and red blood cells; phenolsulphonephthalein output 35 per cent. McClean ratio 57; blood pressure 120 mm.; severe edema; condition improved
2674	M.	3	26	Alk.	93	46	Trace	2.4	0.12	60	0	0	—	Albumin in urine 0.15 per cent; many red blood cells and coarse granular casts; phenolsulphonephthalein output 4 per cent.; blood pressure 88 mm. mercury; uremia; condition improved
2674	Blood...........................				170	116	2.5	5	0.15					

TABLE 8.—Analyses of Spinal Fluid in Meningitis

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Diagnosis and Remarks
					Non-protein N	Urea N	Uric Acid	Creat-inin				Spinal Fluid	Blood	
1845	M.	8	44	Neut.	11	6.5	0	1.0	0.1	8	0	0	...	Serous meningitis; lobar pneumonia; recovered
1778	F.	1½	18	Neut.	15	6.5	0.7	0.5	0.05	50	2+	0	...	Tuberculous meningitis; died
2851	F.	2	..	Neut.	10	4	Trace	2.2	0.08	900	4+	...	...	Tuberculous meningitis; died
2778	F.	5	39	Alk.	30	15	1.2	2.2	0.04	200	4+	...	...	Tuberculous meningitis; died
3303	F.	11	59	Neut.	21	9.5	0	1.9	0.04	100,000	4+	...	...	Cerebrospinal meningitis (diplococcus); improved
4031	F.	9	54	Alk.	21	9.5	0	1	0.06	4,400	4+	...	...	Cerebrospinal meningitis (diplococcus); recovered
2525	F.	6	39	Alk.	15	7.5	0	1.1	0	420	4+	...	...	Streptococcus viridans; died

TABLE 9.—Analysis of Spinal Fluid in Infantile Paralysis

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction	
					Non-protein N	Urea N	Uric Acid	Creat-inin				Spinal Fluid	Blood
4404	F.	1½	19	Alk.	25	12	0	1.7	0.07	24	2+	0	
4523	F.	3	30	Alk.	33	14.5	Faint trace	1.8	0.08	564	0	0	
4808	F	2½	26	Alk.	21	10.5	0	1.5	0.06	6	1+	0	
5049	F.	3	..	Alk.	26	10.5	0	0.5	0.05	14	0	0	
5106	M.	2½	..	Alk.	..	13	0	0.5	0.09	50	0	0	

found, the nonprotein nitrogenous constituents were normal, there was no uric acid present, the sugar content was reduced in both cases, the globulin reaction was positive, and the cell counts were enormously increased. Both patients recovered. In one case of meningitis in which the *Streptococcus viridans* was found, the nonprotein constituents were normal, but sugar was entirely absent from the spinal fluid. The cell count was markedly increased, and the globulin reaction was positive. The patient died.

Five cases of infantile paralysis were examined (Table 9), all in the early stages of the disease. The nonprotein nitrogenous constituents were within normal limits, but a trace of uric acid was found in one case. The sugar content was normal. The cell count was increased in all but one instance and the globulin reaction was positive in two patients, and negative in three.

SUMMARY

Chemical examination of the spinal fluid in ten normal cases in children gave the following results: The total nonprotein nitrogen varied between 17 and 26 mg. per 100 c.c. of fluid, the average being 21 mg.; the urea nitrogen varied between 7 and 13.5 mg., the average being 9.9 mg.; the creatinin varied between 0.7 and 1.5 mg., the average being 0.9 mg. In no case was there enough uric acid present in the spinal fluid to give a positive quantitative test. The sugar content varied within very narrow limits (0.07 and 0.1 per cent), the average being 0.07 per cent. The figures for the nonprotein nitrogenous constituents and the sugar content were lower in the spinal fluid than in the blood, in normal children. The concentration of total nonprotein nitrogen in the spinal fluid averaged 75 per cent. of that in the blood, the urea 82 per cent. of that in the blood and the creatinin 60 per cent. of that in the blood.

The chemical examination of the spinal fluids from diseased children showed the following conditions:

1. In chorea the chemical examination of the spinal fluid for its nonprotein nitrogenous constituents gave results closely paralleling those obtained in normal children.

2. Chemical examination in cases of idiocy, syphilis, epilepsy, and enuresis gave similar results.

3. In acute nephritis without uremic symptoms the total nonprotein nitrogen was slightly increased and uric acid was present in small amounts. In acute nephritis with uremic symptoms the total nonprotein nitrogen, urea and creatinin were markedly increased and uric acid was present in slight amounts. The sugar content was also increased. The figures obtained in the analysis of the spinal fluid were lower than those from the blood.

4. In serous meningitis the nonprotein nitrogenous constituents, as well as the sugar content were within normal limits. In tuberculous meningitis the total nonprotein nitrogen and the urea were normal, but the creatinin was slightly increased. Uric acid was present in every case, but the sugar content was normal or slightly reduced. In cerebrospinal meningitis the nonprotein nitrogenous constituents were normal, but the sugar content was reduced. In a fatal case of meningitis in which the streptococcus was found, the nonprotein nitrogenous constituents were normal and sugar was absent.

5. In the early stages of infantile paralysis the nonprotein nitrogenous constituents, as well as the sugar content, were within normal limits.

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ALKALI AND EARTH ALKALI EQUILIBRIUM IN SPASMOPHILIA *

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In 1913 I published an article[1] on some work done in regard to the relationship of salts in spasmophilia which was the result of experiments on dogs and of clinical observation. In that work I came to the following conclusions:

1. In dogs in which a hyperirritability of the nervous system existed, as shown by the increased electrical irritability, and as produced by removal of the thyroid gland, there is no regular variation in the formula $\frac{Ca}{Na}$ or $\frac{Ca + Mg}{Na + K}$ before and after operation, as shown by metabolic experiment. While in three dogs thus examined there was apparently some support of the proposition that the quotient of this formula is increased during the period of hyperirritability of the nervous system, in the fourth dog no such action could be noticed.

2. In estimating the salt content of the brain of five dogs, the first being a control, there was regularly found a decrease in the calcium content in the thyroidectomized animals. In one instance, however the formula $\frac{Ca}{Na}$ was less than that of the control animal.

3. No variation in electrical irritability or severity of the convulsive period could be demonstrated by intraperitoneal injections of normal sodium and calcium salts in the quantity of from 40 to 45 c.c. of sodium salts, and from 2 to 4 c.c. of calcium salts in twenty-four hours.

4. Even under normal conditions, when carefully estimated, the electrical irritability in dogs varies quite widely.

5. While food containing whey is distinctly irritating to spasmophilic infants, the sodium and potassium salts corresponding in quantity to those contained in the whey do not regularly produce the increased electrical irritability which one would expect were the sodium to be regarded as the irritating substance in the whey.

6. This failure of the sodium and potassium to produce results may be explained either by the fact that the forms in which the sodium and potassium were given, that is, sodium chlorid and calcium chlorid, were not readily absorbed in the gastro-intestinal canal, or that these salts were not in themselves the irritating factors. The latter proposition would seem to be much more probable.

It will be seen, therefore, that these experiments have brought little or no confirmation of the hypothesis that the increased electrical irritability in spasmophilia is the result of a disturbance of calcium and sodium equilibrium.

Since that time numerous articles have appeared on this subject, mostly with the idea of determining whether calcium salts had the effect in spasmophilic infants of reducing irritability.

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* Read before the Section on Diseases of Children at the Sixty-Seventh Annual Session of the American Medical Association, Detroit, June, 1916.

[1] Grulee: Am. Jour. Dis. Child., 1913, **5**, 205.

Freudenberg and Klocman[2] report the reduction of electrical irritability by the use of calcium saccharate, though this was not especially successful, but lipocalcin, a fat-calcium synthetic product, seemed to have a definite effect.

Grünfelder[3] obtained a more rapid and lasting result with calcium-bromid than with sodium bromid in these cases.

Blühdorn[4] lays stress on the fact that only with the use of large quantities of the calcium salts can any effect be produced. With high dosage the action of the calcium occurs within a few hours. He advises the use of from 2 to 3 gm. of calcium chlorid or bromid daily.

In this connection the findings of Behrend[5] are very interesting. Behrend found that magnesium sulphate was of the greatest value. He used an 8 per cent. solution of anhydrous magnesium sulphate. From 15 to 20 c.c. of this solution were given subcutaneously and repeated as often as necessary, intervals being never less than twenty-four hours. The results which he obtained were very satisfactory.

McCallum and Vogel[6] found that the blood of animals in tetany was very poor in calcium and that administration of parathyroid extract did not increase this calcium content. On the other hand, if the extirpation had been incomplete, tetany did not appear and the calcium content of the blood was that of the normal animal. They say:

> In spite of our efforts to shake the theory that tetany is closely dependent on the disturbance of the calcium content of the blood, it is supported by stronger evidence than any other idea, but much remains to be done before a clear conception of the process is reached.

In a recent editorial[7] in the *Journal of the American Medical Association* there appeared the statement:

> The treatment for spasmophilic convulsions is purgation unless the child has already had a severe diarrhea. Breast milk should be given if possible, if the patient is an infant, otherwise the food should be starchy, as barley water or oatmeal gruel. *Some alkali, as potassium citrate, is advisable.* Lime water should be given in teaspoonful doses five times a day.

It is very evident that the writer of this editorial does not believe in the disturbance of the alkali earth-alkali equilibrium in these cases, and it is also quite likely that the advice here given is given because of the hypothesis that spasmophilia may be in some way associated with acidosis. This would seem perhaps to be supported by the findings of Liefmann,[8] who demonstrated an increase of the acetone output of the urine.

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2. Freudenberg and Klocman: Jahrb. f. Kinderh., 1913, **78,** 47.
3. Grünfelder: Therap. Monatsch., 1913, **27,** 416.
4. Brühdorn: Monatsch. f. Kinderh., 1914 (Orig.), **12,** 185.
5. Behrend: Monatsch. f. Kinderh., 1914 (Orig.), **12,** 269.
6. McCallum and Vogel: Jour. Exper. Med., 1913, **18,** 618.
7. Editorial: Jour. Am. Med. Assn., 1916, **66,** 274.
8. Leifmann: Jahrb. f. Kinderh., 1913, **77,** 125.

In regard to the question of the effects of alkali on spasmophilia, two very interesting articles have appeared. Lust[9] reports a case of tetany in a 2-year-old girl, in which he felt that he could recognize a very definite connection between sodium chlorid administered in quantities of 3 to 5 gm. per day and water retention, with, at the same time, a definite increase of electrical irritability. He also saw an increase as a result of administering potassium chlorid in quantities of 0.5 gm. per kilogram per day; the successes noted were on the anodal reaction, not the cathodal.

Brown and Fletcher[10] believe that tetany is due to the retention of water, in which way the sodium salts are held in the body with a resulting increased irritability due to these salts. By diuresis they think one can obtain the best results in these cases, explaining this on the basis of the excretion of the sodium salts from the system.

The work of Zybell[11] is the most extensive on this subject, and I will take up only that part of his work which relates to the effect of the various salts. He noted the action of calcium thirty-four times in twenty-two children, the ages ranging from 2⅘ to 22½ months; five children were in the second year, and eight were less than 6 months old. His patients were frequently troubled with vomiting after the use of a 2.5 per cent. solution of calcium chlorid given in teaspoonful doses at various intervals. In four cases only once was there a decrease of the opening contraction of more than 1 ma. There was no marked difference to be noted with doses as great as 3 gm.; there was no bettering of the laryngospastic or eclamptic seizures; the quantity of calcium seemed to make no difference.

As to the magnesium salts, five cases were tested; a 3 to 5 per cent. solution of magnesium borocitrate was used; no toxic effects were noticed. The reaction in this case was slow. After four hours there was a gradual decrease in the electrical irritability; in no case, however, did the irritability return to normal or change the clinical picture. In testing the sodium salts sodium chlorid and sodium sulphate were used. In five cases examined sodium chlorid 3 to 6 gm. was given; in six and one-fourth hours there was noted an increase of 1 ma. in anodal and cathodal reactions. In two cases, however, the increase was no different from that which had been found in the case in which the food had been withdrawn. With potassium his experiments were carried on with potassium acetate in doses of 30 to 50 c.c. of a 10 per cent. solution. In each case there was a transitory increase of the cathodal opening contraction of from 0.5 to 0.9 ma. After removal of the potassium, irritability immediately went back to its former figure, so that the connection between the increase of the irritability and potassium can scarcely be denied. In a general way it can be said that Zybell's experiments are iconoclastic, since they place in doubt nearly everything which has previously been done on the effects of salts on spasmophilia, and it would seem that this work would need very careful confirmation in order to make it of value.

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[9] Lust: München. med. Wchnschr., 1913, **60,** 1482.

[10] Brown and Fletcher: Am. Jour. Dis. Child., 1915, **10,** 313.

[11] Zybell: Jahrb. f. Kinderh., 1913, **78,** Supplement No. 29.

The observations which I present have been carried out within the past year at the Presbyterian Hospital, Chicago, and consist in a report of six cases in which the effect of the oral administration of large amounts of calcium salts and of sodium and potassium salts were observed. The effects on the cathodal opening contraction will be the only ones noted in this paper. In the early stages in every case it will be seen from the charts that calcium reduced the electrical irritability, while with the sodium and potassium salts there was seen to be an increase in the irritability. The effects of these salts were much less marked as the irritability approached the normal.

Such a case as that of Lillie S. is especially interesting, as the electrical irritability had been at from 2.5 to 3.5 ma. for a full week, when on administrating sodium and potassium for forty-eight hours the electrical irritability rose to 1 ma., then with the administering of calcium the electrical irritability dropped to 4 ma. and the further giving of sodium and potassium had no effect whatever on the curve.

The first of these cases was one which has a very interesting history, as will be noted in the record, and was the one which gave the clue to the observations made later. In this instance the child, who had been on the calcium treatment for tetany, was brought to the hospital suffering with a rather severe pyelocystitis; for this condition large quantities of alkali in the form of sodium bicarbonate and potassium citrate were given, with the result that the temperature was reduced and the pyelocystitis was apparently very much benefited. With the reduction of the temperature we were very much surprised to see the reappearance of the tetany. This again disappeared on the use of calcium salts; the electrical irritability was again raised with a renewal of the alkali.

It is very interesting to note with a careful observation of the weight curves (weight taken at the same time each day) the relationship between the retention of water and the increase of electrical irritability. While this seemed to take place in some instances, in others an increase of electrical irritability was frequently accompanied by a drop in weight. These observations were carried on under like conditions. The electrical irritability was taken at the same time each morning, between the hours of 9 and 10, with the same apparatus, under the same conditions, by the same individual, so that comparative readings were obtained. There was no change of food in the majority of the cases, and in none of the cases was there to be noted a gastro-intestinal disturbance.

For the purpose of control, three nonspasmophilic persons were given like doses of sodium and potassium salts with no demonstrable effects upon the electrical irritability. It has been thought for some time by most observers that large quantities of calcium salts decreased electrical irritability and that removal of these salts would be followed by a return to an increased electrical irritability. It is quite likely that this return depends somewhat on the length of time of the administration of the calcium salts and the severity of the spasmophilic condition. It does not seem likely, however, that the simple removal of the calcium salts would always be followed by the definite reaction which is shown in these six cases in the early stages after the administration of sodium and potassium salts. Certain cases, such as that of Lillie S., speak distinctly against such an interpretation. While I do not feel that one would be justified in stating that the observations recorded give definite proof that there is a direct relationship between sodium and potassium salts and increased electrical irritability, or that spasmophilia rests on the question of equilibrium between the calcium and magnesium salts on the one hand and the sodium and potassium salts on the other, still it seems to me that the results here recorded do speak very strongly for some definite relation between increased electrical irritability and retention of sodium and potassium salts.

I recognize that much work must be done in order to establish such a fact. This cannot be done without exhaustive metabolism experiments or without examination of brain tissue under somewhat ideal conditions. It would seem to me, however, that if there is such a definite relation between the sodium and potassium on the one hand and calcium and magnesium on the other, the action of the sodium and potassium salts is not due primarily to retention of water in the system; or, if such is the case, we have no direct evidence to support such a theory and that we would have to suppose that in the observations here noted there had been marked destruction of tissue accompanied by distinct retention of water in those instances in which the electrical irritability was increased and the weight reduced.

CASE 1.—Fay K., aged 6½ months, entered the Presbyterian Hospital April 8, 1915, assigned to Dr. Grulee, complaining of fever, general debility, and loss of weight. Three weeks previous to entrance the mother had noticed that the child, who up to that time had been perfectly well, began to grunt and acted as if distressed. She had chills and sweats, the temperature went up to 103.5, and she apparently had a convulsion, though she had no more after that. The child was put in warm blankets, and the condition seemed to improve, though she would take only about half her feedings, and three days later did not eat anything. The mother thought that the pain was in the head at that time, though enemas seemed to give the child some relief.

It was about this time that I first saw her, when she was taken to a hospital in Kenosha, Wis. The diagnosis was that of severe infection of the nose and throat. There was considerable vomiting at this time. The temperature fluctuated between 98 and 104. Examination of the ears proved negative. The condition apparently cleared up. About a week after the onset the child again developed a fever and when seen again by me in consultation she had a very typical carpopedal spasm, quite marked. This cleared up on the use of the usual treatment, calcium lactate, etc., when the child a third time developed a high temperature, and this time was sent to the Presbyterian Hospital, where she entered April 8, 1915. Previous to entrance the food had consisted of mother's milk with the addition of Mellin's food; later, Mellin's food alone.

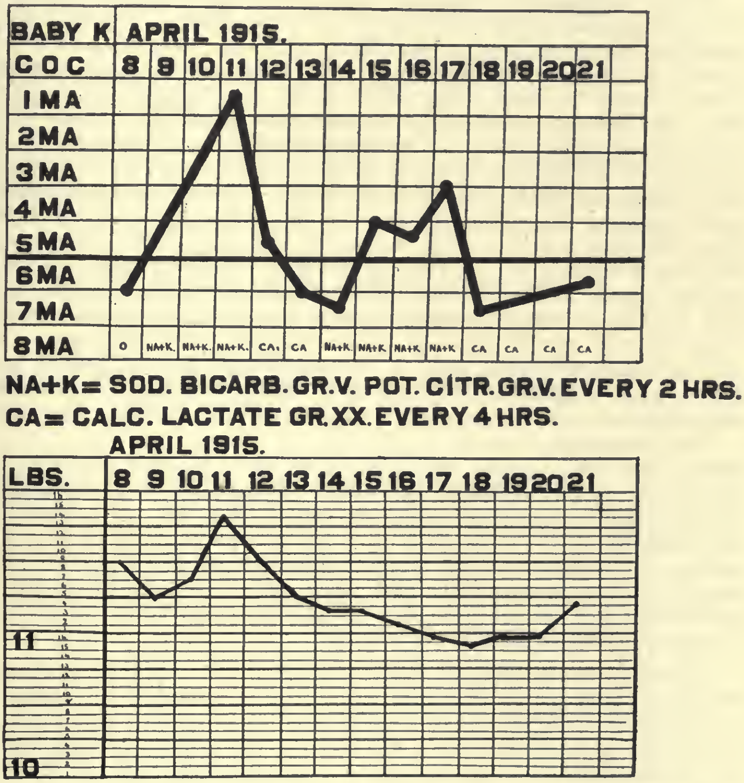


Fig. 1.—Record of Fay K. (Case 1), aged 6½ months. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

Of course the Mellin's food was put up according to the formula advised on the package, which included a fair quantity of milk. The stools could not be noticed because of the frequent enemas given for gas. Curds, however, were often seen, and constipation was never present. The urine was ammoniacal and stained the diaper. Three days before entrance the child did not urinate for sixteen hours. The bladder was distended and the baby seemed distressed. There was no apparent pain on urination. The urine seemed to cause some irritation in the genital region and about the buttocks. Other history, both of the child and mother, was negative.

Physical examination showed a rather apathetic child, undernourished. The head was well formed in its general outline. Posteriorly and below the occiput was a depressed area about the size of a dollar. On gentle pressure this could be slightly indented (craniotabes). The sutures were prominent. The anterior fontanel was about 2 inches in width. The ears and eyes were negative. There was a slight nasal discharge. The lips were dry and parched. The neck and chest were negative. The abdomen was at times flat and then distended with gas. The liver and spleen were not palpable. The extremities were negative. The reflexes were not increased. The surface of the body was extremely dry and hot and the skin somewhat scaly. The palms and soles were thickened, and the skin on the palms appeared calloused.

Clinical notes: On April 8 the electrical irritability was taken, and the cathodal opening contraction was 6 ma. The child on April 9 was put on potassium citrate and sodium bicarbonate, 5 grains each every two hours. On April 11 a typical tetany was present. The hands and feet were contracted with a tonic spasm. Edema was present, due to the contraction. Electrical irritability was greatly increased. The potassium citrate and sodium bicarbonate were stopped, and the child put on 20 grains of calcium lactate every four hours. By April 12 the tetany was found to be much less rigid, and the child was in much better condition. On April 13, on the same treatment, the child was in good condition, the edema was less and the tetany was much decreased. The child was then put on sodium and potassium again, with an increase of the electrical irritability on April 17 up to 3 ma. The child was then put back on calcium lactate, with a decreased electrical irritability. She left the hospital on May 10, the electrical irritability on May 6 having been normal. From April 17 on the child got 20 grains of calcium lactate every four hours. The child was on breast milk until April 17, when the food was changed to part breast milk and part albumin milk. On April 18 all the food became albumin milk, and this continued, with the exception of two days, until the child went home.

The temperature went above 100 only once during her stay in the hospital, when it was 100.2. From April 8 to April 14 the temperature ranged between 99 and 100. After that it was well within normal limits. On entrance the blood showed 22,000 white cells, and 65 per cent. hemoglobin. On April 19 the red cells were 5,150,000, white 11,600. The Wassermann was negative on two examinations. On entrance the urine showed about 10,000 leukocytes per cubic millimeter. This gradually cleared up under the use of hexamethylenamin. The catheterized specimen of urine showed staphylococcus in pure culture. The stool examination showed nothing of interest.

Case 2.—Lillie S., aged 7 months, entered the Presbyterian Hospital Feb. 17, 1915, on the service of Dr. Grulee. The complaint was that the child had had convulsions. These were first noticed three months previous to entrance, and had continued up to the time of entrance. There had been as many as ten a day, and at times the child had gone as long as a week without any. When the child was in one of these convulsions the eyes rolled and twitched, and the arms and neck muscles twitched. The seizure was usually not severe. The feeding had always been from the breast every three hours. The condition had always been good, the patient never having been sick. The bowel movements were normal.

On physical examination the patient was found to be very well nourished, well rounded, and fat. The head was round, and the anterior fontanel was about 1 inch in greatest diameter. The face was negative, the mouth and throat clear. There were no teeth. The abdomen and limbs were negative, the thighs extremely fat, the skin clear and normal, and there were no palpable lymph glands. The reflexes were normal. It is noted that on February 20 an enormous number of the *Bacillus coli* were found in the urine. The child during her first stay in the hospital showed a temperature ranging between 98 and 100.4. The apparatus for testing the electrical irritability at this time was out of order, so that this was not taken. She was given chloral hydrate rectally 1 grain every four hours. The interval was gradually increased to six hours and then to eight. However, the dose was increased to 2 grains when necessary, and it was found necessary to give the child for the first three doses 2 grains. Calcium lactate, 20 grains every two hours, not to exceed six doses, was begun on February 20. It was then continued twice a day thereafter for three days. The child was breast fed throughout. Hexamethylenamin to the amount of 1 grain was begun on the 22d. At this time the blood showed 5,200,000 red cells, 8,100

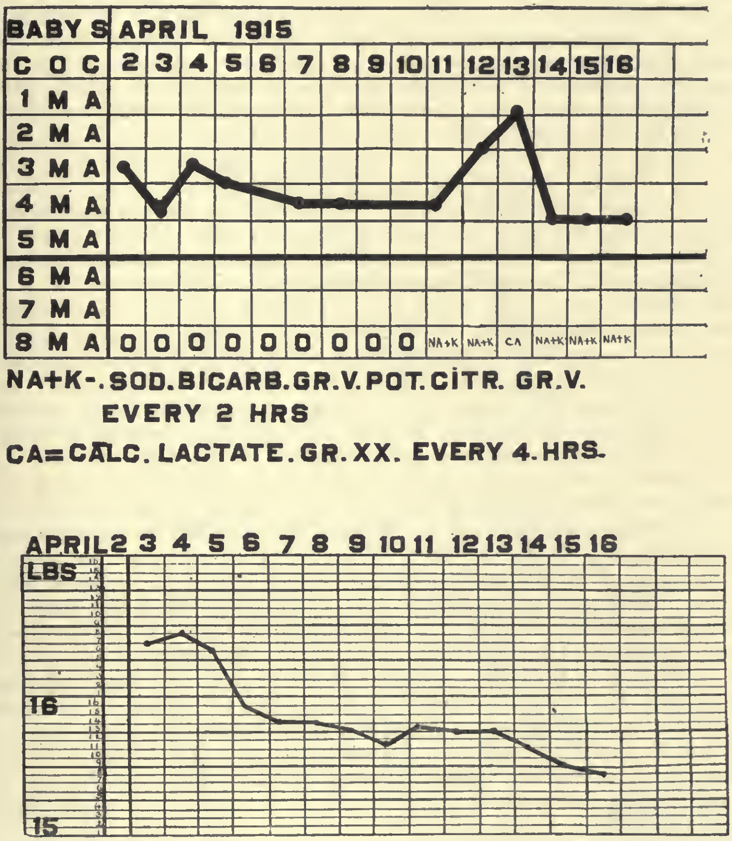


Fig. 2.—Record of Lillie S. (Case 2), aged 7 months. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

white and 85 per cent. hemoglobin. On February 18 the urine showed about 100 leukocytes per cubic millimeter, and a slight amount of nucleo-albumin. On the 20th the number of leukocytes was 250 per cubic millimeter, and the nucleo-albumin had increased in quantity. On March 2 there were to be found 500 cells per cubic millimeter. The child left the hospital on March 9 and returned again on the 18th with a renewal of the convulsions.

This history was that after leaving the hospital the child had had no convulsions until just previous to entrance, when they had begun to come at the rate of four a day. The child was still nursing from the breast, and there was no other complaint. This child on entrance on March 18 was given 1 grain of chloral hydrate per rectum every four hours, and 20 grains of calcium lactate every three hours. The first electrical irritability test was made on March 2, when it was found that the cathodal opening contraction equaled 3 ma. Until March 11 the electrical irritability daily ranged not lower than 2.5 and not greater than 4 ma. For March 7, 8 and 9 the electrical irritability was 3.5 ma. On March 11 the child was put on 10 grains of sodium bicarbonate and 10 grains of potassium citrate every four hours, and the calcium lactate was stopped. On March 12 the cathodal opening contraction equaled 2 ma., and March 13 1 ma. The sodium and potassium were stopped and the child was again put on the calcium lactate, the amount previously given. On March 14 the cathodal opening contraction equaled 4 ma. The calcium was again stopped, and the sodium and potassium given a second time. From this time on the electrical irritability never went below 4 ma., the child remaining within normal limits until May 25. Until May 24 the child was given 5 grains each of sodium bicarbonate and potassium citrate every four hours. This was continued until May 29. On May 25 the cathodal opening contraction equaled 4.5 ma., on May 28 it equaled 4.5, and on May 29 5 ma. The amount of sodium bicarbonate and potassium citrate was then increased to 10 grains each, with the result that by June 5 the electrical irritability had fallen to cathodal opening contraction equal to 4 milliamperes. There had been a gradual and steady reduction.

The clinical notes show very little during this period. The temperature ranged between 98 and 100. On April 2 it rose to 103, but came down again within a few hours, and continued between the previous limits until the 17th, when the temperature again rose to 104. The highest on the following day was 103, then it dropped to normal and remained practically normal until May 7, when the child had a continuous temperature ranging between 101 and 102, until May 15. Then the temperature again came to normal and remained so until May 24, when it rose to 101.6, and on the 25th it went to 101.8, coming down to normal on the 26th, remaining normal on the 27th. But on that day it rose to 103.2, coming down again on the 30th and remaining so during the remainder of the child's stay in the hospital. There is no record of a convulsion after the child entered the hospital except that on April 3, at 9 a. m., just following the acute febrile stage, the child had one convulsion, which lasted four minutes, another lasting three minutes at 4:30 p. m., and at 7:45 p. m. another one lasting two minutes. The child during her stay at the hospital always showed some leukocytes in the urine, which probably accounts for the irregularity in temperature. For instance, on May 10 the number of leukocytes was found to be 5,000 per cubic millimeter. There was a leukocytosis of 16,200 on that day. On April 28 the blood count was 4,500,000 red cells, 15,500 white, of which 64 per cent. were small lymphocytes, 11 large lymphocytes, 4 transitional, and 46 polymorphnuclear neutrophils. On May 12 the child showed 9,000 leukocytes, on May 29 20,700.

There are no special clinical notes on this case except that on April 17 it was noted that though the child had been for seventy-two hours on sodium and potassium the urine was still acid.

Case 3.—Olga K., aged 5 months, entered the Presbyterian Hospital on the service of Dr. Grulee December 2, 1915, with a history of convulsions, cold in the head, and slow gain in weight. She had been born at home on July 7 previously, a midwife attending, the birth weight being 11 pounds, in a normal labor of two hours' length. The child had never been nursed, but had been bottle fed from birth. She had been fed according to the directions of the Infant Welfare Society. There were three to four stools a day, apparently of good consistency, and castor oil was used quite frequently. There were three other children in the family, aged 15, 13, and 11 years, respectively, all in school. The convulsions had begun the day before entrance, the child having had fifteen in the course of twenty-four hours. During an attack the infant grew rigid, the fists were clenched, the eyes rolled, and there was cyanosis. She coughed after the convulsions for a few minutes, and then grew quiet. The child had had no convulsions for thirty-three hours previous to entrance. The gain in weight had been slow. She had had a cold in her head for five weeks, which had been growing worse, and there was some nasal discharge. Examination showed a fairly well-developed and fairly well-nourished child. Cradle cap was present, and the skin of the body was rather dry and easily irritated. All the glands, including epitrochlears, anterior and posterior cervicals, axillary and inguinal, were palpable. With this exception, nothing was noted of any value on physical examination. On December 4 her electrical irritability showed cathodal opening contraction approximately normal. On December 3 her blood count showed 5,260,000 red cells, 7,800 white, and 90 per cent. hemoglobin. The urine was negative, as was the throat culture. The Wassermann, both on the blood and the cerebrospinal fluid, was negative. For two weeks, beginning December 8, she was given 1/20 grain protiodid of mercury three times a day.

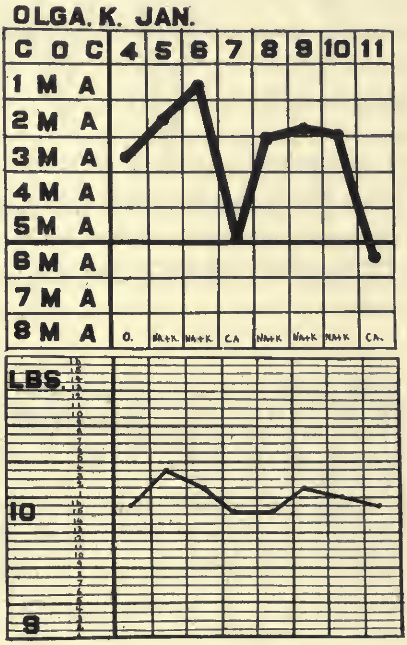


Fig. 3.—Record of Olga K. (Case 3), aged 5 months. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

Her weight on entrance was 9 pounds, 9½ ounces. At the time of leaving on January 31, 1916, it was 10 pounds 3½ ounces. On January 4 her electrical irritability was taken, and it was found that she had a cathodal opening contraction equal to 2.5 ma. She was given 10 grains each of sodium bicarbonate and potassium citrate every two hours for the next two days, with the result that on January 5 the increase of electrical irritability was shown in a cathodal opening contraction equal to 1.5 ma., and on the 6th it equaled 0.5 ma. On January 6 the child was given 10 grains of calcium lactate every four hours, with the result that the cathodal opening contraction was raised to 5 ma.

Calcium was then discontinued, sodium and potassium being given again on January 8, 9 and 10. The reactions became 2, 1.75 and 2 ma. on the three respective days.

A slight laryngospasm was noticed on January 8, more marked on the next day, and less marked on the 10th. On this last day calcium was given again, with the result that on the 11th the cathodal opening contraction became 5.5 ma.

The child left the hospital on January 31 because of the development of a gonorrheal vaginitis.

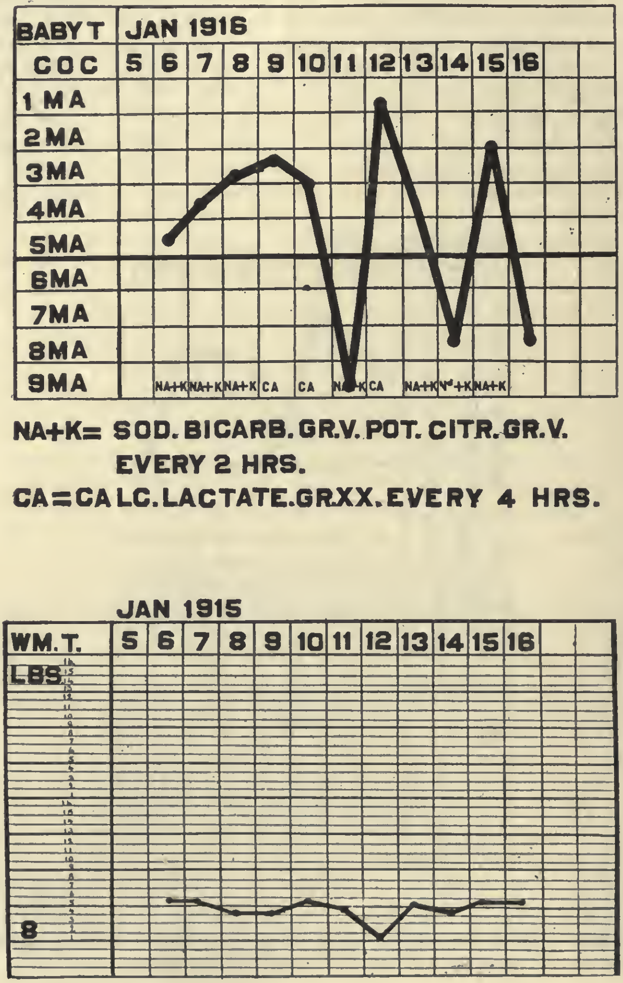


Fig. 4.—Record of William T. (Case 4), aged 3 months. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

Case 4.—William T., aged 3 months, entered the Presbyterian Hospital the first time on Dec. 9, 1915, on the service of Dr. Grulee, with the complaint of emaciation and constipation. The history obtained was imperfect, as it could be secured only through an interpreter. The child was born on September 2, 1915. It was the fifth child, weighed 9½ pounds (?), was born in two-hour normal labor, with midwife as attendant, and with vertex presentation. The child was bottle fed. The mother had nursed none but the first two children.

The child had been at an infant welfare station, where it had received its food. About a month previous to entrance, probably before having been taken to the infant welfare station, the child had had severe dysentery, from which it had not completely recovered. The emaciation had lasted from the time of the dysentery, as had also the constipation. Constipation had been treated with castor oil. There had been for a short time previous to entrance an alternating of constipation and diarrhea, the number of stools varying from one to ten or twelve a day. The stools were usually green, and varying from liquid to hard. The child showed a very irregular weight curve. The weight at entrance was 7 pounds 10½ ounces and when he left 8 pounds 8 ounces, his stay in the hospital having been about six weeks. During that time the food consisted, with the exception of the first day, of albumin milk, which was gradually increased from 18 to 24 ounces, and dextri-maltose increased from ½ to 1 ounce. From January 3 on there had been added ¼ ounce of flour ball to the day's feeding. The temperature showed a tendency to be rather subnormal, though occasionally points above the normal were seen. On December 10 the blood showed 5,880,000 red cells, 22,000 white and 80 per cent. hemoglobin. The urine was negative. A throat culture showed no diphtheria. On December 13 a few pus cells were found in the urine. This continued for a few days, after which the urine was negative. The number of pus cells in this case could hardly constitute a reason for calling the case one of pyelocystitis. On January 13 there is a clinical note that a furuncle on the outside of the right heel was incised and considerable pus removed. With this exception, the course of the child in the hospital was without incident, except for the electrical irritability. This increased electrical irritability was not accompanied by any signs of spasmophilia, although at times it was quite marked. On January 6 the cathodal opening contraction equaled 3.5 ma. Under sodium bicarbonate and potassium citrate, 10 grains of each every two hours, the cathodal opening contraction became 2.5, 1.7 and 1.25 ma. on January 7, 8 and 9, respectively. Calcium lactate, 20 grains every four hours, was now begun, with the result that on the 10th and 11th the cathodal opening contraction equaled 2 and 8.5 ma. on the two respective days. Again sodium bicarbonate and potassium citrate were given, and on January 12 the irritability was increased to 0.9 ma. As a result of the readministration of calcium lactate the irritability fell on January 13 to 3.5 ma. The sodium and potassium compounds were again adminisistered as before, but the irritability on January 14, 15 and 16 was over 5, 2 and over 5 ma. on the three respective days.

Case 5.—Euphrosene G., aged 16 months, entered the Presbyterian Hospital on December 16, 1915, on the service of Dr. Grulee. She was the sixth child, born of a rapid normal labor, vertex presentation, weight 8½ pounds. She was fed three months on the breast, and then fed on modified milk for sixty-seven days previous to entrance. The mother said that the child had been drowsy and had slept too much. She also made strange noises while breathing. She had had a slight cough for the week previous to entrance, and some sneezing. There were some fever and chills. No treatment was given for three days previous to entrance. During her waking periods she seemed very much disturbed as she cried almost constantly. On physical examination the child was found to be well nourished and well developed. The fontanel was open. There were some few râles in the lungs posteriorly. The liver and spleen were not palpable, nor was there anything about the extremities except the lesions on the skin. These lesions were discretely distributed over the trunk posteriorly, left upper arm, and extended on surface of the legs. They were pigmented, at times crusted, small papules, from 2 to 4 mm. in diameter. There was some evidence of scratching. The posterior cervical, the axillary and the inguinal glands were palpable. Electrical irritability on the day of entrance 5 o'clock in the afternoon showed cathodal opening contraction equal to 4.5 ma. The child on entrance was given 10 grains of sodium bicarbonate, and 10 grains of potassium citrate every two hours. On December 17 and 18 the irritability was increased to 2.5 and 0.75 ma., on the two respective days, and there was a definite laryngospasm. On December 18 the sodium and potassium were dropped and calcium lactate, 15 grains every four hours was given. On the 19th the electrical irritability was 6 ma. On December 19 the sodium bicarbonate and potassium citrate were again given. The electrical irritability became 4.5, 3.5 and 2 ma. on December 20, 21 and 22, respectively. On the 22d calcium lactate was again given. On the 23d the electrical irritability was cathodal opening contraction 7 ma. The calcium lactate was then stopped and the child given cod liver oil and phosphorus. On the 29th the electrical irritability showed 8 ma. During the time when the child was under observation for electrical irritability there was no change in the food. The weight during that time showed a steady decrease, except on the first two days (see weight curve). There was no increased fever, temperature remaining normal throughout the whole course. The blood count showed 5,430,000 red cells, 11,300 white and 75 per cent. hemoglobin. A throat culture proved negative for diphtheria. The urine was negative throughout.

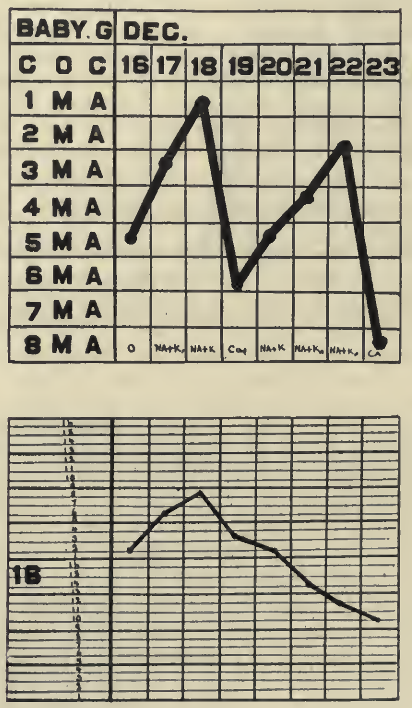
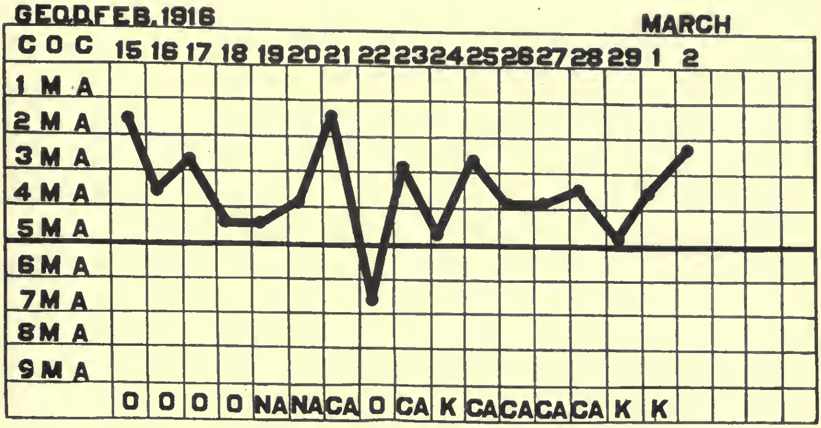


Fig. 5.—Record of Euphrosene G. (Case 5), aged 16 months. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

Case 6.—George D., aged 8 months, entered the Presbyterian Hospital on Feb. 14, 1916, on the service of Dr. Grulee, with the complaint of convulsions, inability to cry, and loss of weight. The child was born on the previous June 9, weighing 6 pounds 12 ounces. He was the second child, born of an eight-hour normal labor, breech presentation. He was breast fed for six weeks every two hours, then changed to artificial feeding because of insufficient breast milk. First he was put on milk and barley water every two hours, then on a formula of certified milk for two weeks. The stools became bad and the food was changed to a different formula and prepared food used, always given every two hours. Within the four days previous to entrance the child had been on a mixture of 20 ounces of whole milk, 10 ounces of water, ½ ounce of dextri-maltose, five feedings of 6 ounces each. The stools at the time of entrance were regular and normal. The convulsions began five weeks previous to entrance.



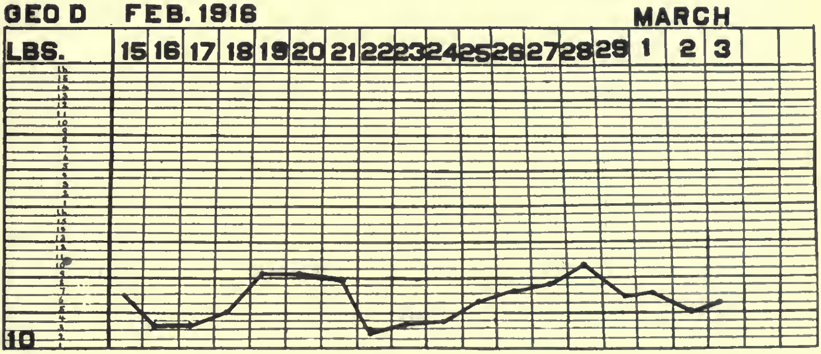


Fig. 6A.—Record of George D. (Case 6), aged 8 months. First period. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

There had been three on the first day, and three on successive days. There had been none after that time. The child, however, since the onset of the convulsions, had shown an inability to cry. It made the effort, but got very short of breath and could make no noise. Even before the convulsions occurred this tendency was present. There had been an indefinite loss of weight since the convulsions first occurred. For the previous few days the child, however, had gained 10 ounces. On examination he proved to be an emaciated boy, who showed a very evident laryngospasm. The skin was negative except for a reduction of tissue turgor. The lymph glands were palpable in the anterior and posterior cervical, axillary, epitrochlear, intercostal, and inguinal regions. The head and the thorax were negative, and the abdomen negative except for right inguinal hernia. On February 18 it was noted that the von Pirquet was negative. On February 22 it was noted that the spinal dulness reached to the seventh dorsal spine. On March 4 the child showed increased râles over the chest posteriorly, the breath was labored, and there was a frequent harrassing cough. The child seemed quite sick, and a diagnosis of bronchopneumonia was made. On March 5 the von Pirquet was again negative, and on the 7th it was noted that the lungs were clear. On the day of entrance the red blood cells

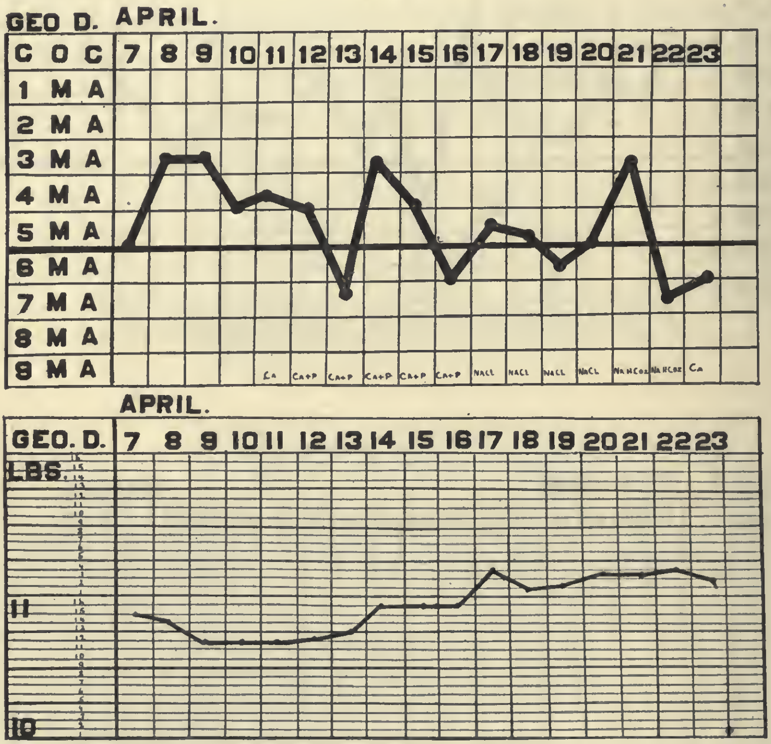


Fig. 6B.—Record of George D. (Case 6), aged 8 months. Second period. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

numbered 5,820,000, white cells 27,450, and the hemoglobin 85 per cent. A throat culture was negative for diphtheria and a urine analysis was negative. On March 3 the leukocyte count was 18,500, with a differential count of 61 per cent. polymorphonuclears, 31 per cent. small lymphocytes, and 1 per cent. basophils. From the time of entrance, when the child weighed 10 pounds 8 ounces, until March 22, when the child weighed 11 pounds 6 ounces, the weight was irregularly upward. On the day of exit, April 23, the child weighed 11 pounds 1 ounce. The temperature on the whole was normal; on February 21, 22 and 23 there was a slight fever, running as high as 101.8, when the child developed a slight cold. The other febrile period was that which occurred during the attack of bronchopneumonia, which was at its height on March 4. With these exceptions the temperature was within normal limits, possibly rising to 100 at times. Table 1 is a record of the electrical irritability, together with laryngospasm.

TABLE 1.—Record of Electrical Irritability of George D., Case 6

Date, 1916	Dosage	Irritability, K.O.C., Ma.	Symptoms
2/15		1.5	Laryngospasm
	No medicine		
2/16		3.5	Laryngospasm
2/17		2.75	Laryngospasm
2/18		4.5	Laryngospasm
2/19		4.5	Laryngospasm
	$NaHCO_3$ 10 gr. every 2 hr.		
2/20		3.8	Laryngospasm
2/21		1.5	Laryngospasm
	Ca Lactate 15 gr. every 4 hr.		
2/22		6.5	Laryngospasm not so marked
	No medicine		
2/23		3.0	Pharyngitis
2/24		5.0	
	K. Citrate 10 gr. every 2 hr.		
2/25		2.75	Marked laryngospasm
	Ca Lactate		
2/26		4	No laryngospasm
2/27		4	No laryngospasm
2/28		3.5	Laryngospasm
2/29		5.0	Some laryngospasm
	K		
3/1		3.5	Marked laryngospasm
3/2		2.25	Marked laryngospasm
	No medicine		
3/3		3.0	Marked laryngospasm
4/7		5	
4/8		2½	Slight laryngospasm
4/9		2½	Laryngospasm
	Ca		
4/10		4	Laryngospasm
4/11		3.5	No laryngospasm
	Ca and P*		
4/12		4.0	No laryngospasm
4/13		over 5	No laryngospasm
4/14		2.5	No laryngospasm
4/15		4.0	Slight laryngospasm
4/16		6	No laryngospasm
	NaCl 10 gr. every 2 hr.		
4/17		4.25	No laryngospasm
4/18		4.5	No laryngospasm
4/19		5.5	No laryngospasm
4/20		5	No laryngospasm
	Na bicarbonate		
4/21		3.5	No laryngospasm
4/22		6.5	No laryngospasm
	Ca		
4/23		6	No laryngospasm

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* Phosphorus was given in the form of cod liver oil and phosphorus (1/120 per cent.) 1 c.c. in each bottle of food.

CONTROL CASES

In order to see whether it would be possible to produce increased electrical reactions by the addition of sodium and potassium on persons who had never at any time shown increased electrical irritability and gave no history of spasmophilia, three children were tested, Mary P., aged 4 months, Annie R., aged 9 months, and Howard M., aged 18 months.

On January 6 in the case of Mary P., the electrical irritability was taken and was found to be, cathodal opening contraction equal to 10.5 ma. The child was given 10 grains of sodium bicarbonate, and 10 grains of potassium citrate every two hours, and on the 7th the electrical irritability was found to be 8 ma., on the eighth, 7, and on the 9th, 8 ma.

In the case of Annie R., Jan. 7, 1916, the cathodal opening contraction equaled 7 ma. Sodium bicarbonate and potassium citrate, 10 grains each were given every two hours for the next three days, with the result that in each instance the irritability remained over 5 ma.

In the case of Howard M., on the 7th and 8th the cathodal opening contraction was found to be over 5 ma. On the 8th the child was given 10 grains each of sodium bicarbonate and potassium citrate, without any influence on the electrical irritability. This was discontinued on the next day.

ACROCEPHALY

WITH A REPORT OF TWO CASES *

PHILIP LEWIN, M.D.
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Acrocephaly, or tower head, is the term applied to that syndrome consisting of a dome-shaped skull, with characteristic Roentgen-ray findings, exophthalmos and optic nerve changes, associated with some minor abnormalities, such as a high, arched palate and deformities of the hands or feet. Acrocephaly is synonymous with *thurmschädel, Spitzkopf,* steeple head, turret skull, *turritum caput, tête à la thersite.* When combined with deformities of the hands or feet the name acrocephalosyndactilysm is applied. Previous to 1911 Fletcher[1] found there had been reported between eighty and ninety cases. Von Graefe[2] in 1866 first definitely recognized and described the condition. Since then Michel,[3] J. Hirschberg,[4] Enslin,[5] Patry[6] and others have reported cases.

The etiology is obscure. The most probable cause is a premature ossification of the cranial sutures, but the underlying cause is unknown. There is not even a good theory. Syphilis does not seem to play an important part. In most of the reported cases the patients had had measles, but that is evidently not significant. Race does not predispose. Rickets has been found in some and absent in others. Males predominate in the reported cases. Heredity might play a rôle. J. Hirschberg reports a patient whose maternal grandfather was similarly affected. Weiss and Brugger mention two oxycephalic brothers seen by Oeller. Hanotte[8] states that Hamy saw two oxycephalic sisters. Fletcher reports a patient whose mother had a malformed head, exophthalmos and defective vision.

The malformation has been ascribed to intrauterine meningitis, which is supposed to cause early union of the sutures. Almond's[9] patient cut two teeth before 3 months and sixteen before 1 year. He considers that the early appearance of teeth brings up the possibility of some hyperactivity of the osteoplastic tissue. Early union of sutures, especially coronal and sagittal, leads in some cases to microcephalic oxycephaly. In some cases, as in Almond's, some of the fontanels and sutures, the points of weakest resistance, apparently have yielded to increased pressure put on them, and this has led to the formation of encephaloceles (Fig. 3). The malformation of the orbit is generally supposed to be due to synostoses, affecting the base of the skull. Whether the narrowing of the optic canal is due to pressure downward and forward of the superior orbital plate, or whether the atrophy of the optic nerve is first caused by intracranial pressure, and the narrow optic canal is simply a lack of development corresponding to the small size of the nerve, is a matter of dispute.

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* Submitted for publication July 21, 1916.

[1] Fletcher: Quart. Jour. Med., 1910-1911, **4,** 385.

[2] Von Graefe: Arch. f. Ophth., 1866, **12,** Part 2, p. 114.

[3] Michel: Arch. f. Heilkunde, 1873, **14,** 39.

[4] Hirschberg: Centralb. f. Augenheilk., 1883, **7,** 1.

[5] Enslin: Ophthalmoscope, 1904, **2,** 233.

[6] Patry: Thèse de Paris, 1905; Recueil d'ophthal., Paris, 1906, Series 3, **28,** 156, 158; Ann. d'oculistique, Paris, 1906, **135,** 314.

[7] Weiss and Brugger: Arch. Ophth., 1895, **24,** 55.

[8] Hanotte: Thèse de Paris, 1898.

[9] Almond: Alienist and Neurol., 1910, **31,** 487; Bristol Med.-Chir. Jour., **28,** 118, 1910, p. 1377.

Very few cases have been recorded with postmortem examination. H. Power[10] reports a full-term child brought to the hospital when thirty-six hours old, who died within thirty days. It was a typical case. The postmortem examination was as follows:

> Sagittal section was made through the vertical meridian of the right cornea. The orbit was extremely small, the entire depth being 2.5 cm. from the inferior border to the optic foramen. The floor of the orbit was horizontal, but the roof was almost vertical in position; it was formed mainly by the lesser wing of the sphenoid behind, and by a small portion of the orbital plate of the frontal bone in front. This roof was directed upward and forward at an angle of more than 45 degrees and was continuous with the vertical plane of the frontal bone, into which it passed with only a small projection to mark the orbital edge. A perpendicular line from the front of the vertical portion of the frontal bone fell entirely behind the globe. The whole orbit was too small to receive the globe of the eye. From its entrance at the optic foramen the nerve ascended sharply, and remained in close relation with the roof of the orbit till it bent downward to enter the sclerotic. The height of the orbit at its extreme anterior part was 32 mm., that of the normal skull for this age being 20 mm., so that the orbit was too wide at its opening and too shallow from before backward.
>
> The head was prolonged upward into a blunt cone; the result of this was to change the normal position of the convolutions of the brain, the frontal convolution and corpus callosum being perpendicular in direction.
>
> The anterior fontanel was present and open.

The striking features of a case are the deformity of the skull and the exophthalmos. For characteristic deformity of the skull see Figure 3. The exophthalmos may be extreme. Vision may be unaffected or totally destroyed. Optic atrophy is the most constant ophthalmologic finding. The disks are usually grayish, bluish or ivory with irregular edges, the arteries thin, the veins dilated and tortuous. Choked disks are present in some cases. In forty-two cases Enslin found the atrophy was postneuritic in thirty-six; in two it was regarded as primary.

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[10] Power, H.: Tr. Ophth. Soc. United Kingdom, 1894, **24,** 212.

Friedenwald[11] found postneuritic atrophy in nine of twelve cases. Occasionally there are pigmentary changes in the retina near the disk. Myopia is common.

There is usually a high-arched palate. In Almond's case it was impossible for the finger tip to reach the apex of the arch.

The Roentgen-ray findings are definite and characteristic. There is dimpling of the inner table of the skull (Figs. 3, 4 and 7).

The mentality may or may not be affected. Potts[12] states that in examining thousands of mentally defective patients he met with only two cases of acrocephaly. Hearing is usually unaffected, taste rarely affected. Meltzer found smell completely lost in twelve out of twenty cases. Headache may be frontal, vertical or occipital. Vertigo may or may not be present. The hairy scalp is frequently raised above the normal level, although the writer has seen striking examples of that condition with no other sign of acrocephaly. Because of the exophthalmos which is present in all marked cases there is failure of closure of the lids, with lacrymation and conjunctivitis.

Dislocation of the eyeball is not uncommon. Almond reports a case of a child in whom dislocation of either eyeball occurred occasionally when the child cried. Divergent strabismus is frequent and nystagmus is found in the majority of cases.

The thumbs may be flattened. There are all grades and kinds of associated abnormalities of the hands and feet. Gadelius[13] reports five cases with syndactylism. Poor extension of the elbows and shoulders has been noted.

There is frequently deflection of the nose. The complexion may be muddy. The patient is usually a mouth breather, and early dental caries has been noted in many cases.

Case 1.—E. S., a white girl, 14 years of age, was admitted to Wesley Memorial Hospital on the service of Dr. Kanavel, having been referred by Dr. Patillo. The history, as I obtained it from the mother, showed that the girl was brought to the hospital because of (1) blindness, (2) weakness and small size of right arm, and (3) enlargement of the head. The early history showed that the patient had been a full-term baby, born without the aid of forceps. Her mother was in good health during the pregnancy, and although she was in labor only six hours she says it was a "hard labor." The child was born two hours after the membranes had ruptured. The mother was given chloroform. There was no asphyxia neonatorum. The child's head was normal in size and shape. She was breast fed for one year. She was the tenth child in a family of thirteen children.

She was perfectly well until she was 3 months of age, when she became ill. The trouble seemed to be "all in her head, because she was always rubbing her head and scratching her ears." There were no convulsions, opisthotonos, rigidities, or cough. There was a moderately high fever. The child was sick about two weeks and thenceforth "always seemed to have a headache." There was no epidemic of any disease at this time.

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[11] Friedenwald: Am. Jour. Med. Sc., 1898, **55**, 529; Proc. Roy. Soc. Med., Child. Sec., 1909, **2**, 277; ibid., Clinic. Sec., 1909, **2**, 115.

[12] Potts: Rep. Soc. for Study of Dis. in Child., London, 1908, **8**, 407.

[13] Gadelius, Bror: Nord. med. Ark., 1915, Division 2, **48**, 1-30.

When 5 months old, for no apparent reason "her eyes gradually began to bulge and her head seemed to get large on top." At 5 or 6 months she had a tooth and at 12 months had ten. She sat up at 6 or 7 months and could walk and talk at 1 year. Until 18 months old she could walk and play like other children, but after that time her mother noticed that she could not see well. She would reach for objects and miss them. If she were given an object she would have to bring it close to her eyes in order to see it. Both eyes seemed to be affected simultaneously and to the same degree. At the 19th month her mother thought she could not see at all. Her ears never caused trouble, except when she caught cold, at which times she was slightly deaf.

At the age of 3 years she was taken sick with four or five convulsions, one of which was severe. The attack lasted two weeks, at the end of which time she was as well as previously, except for diminishing size and strength of the right arm as compared with the left

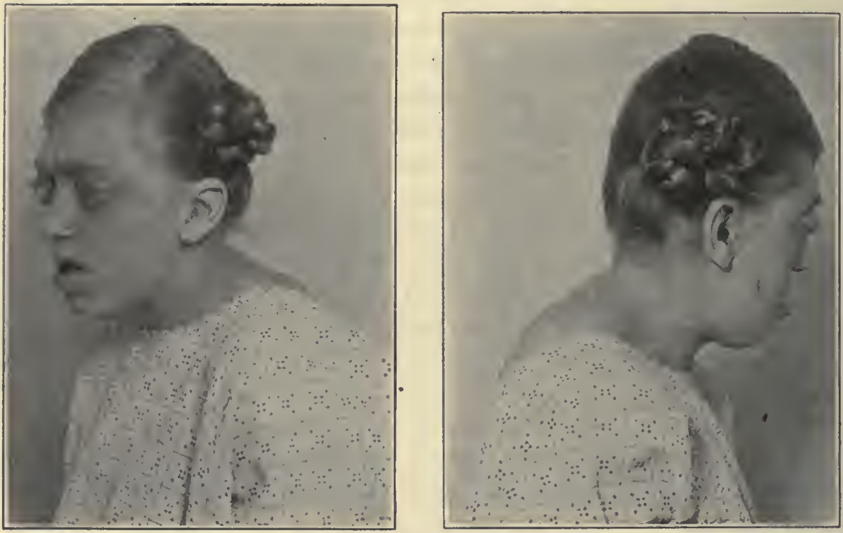

Figure 1 Figure 2

Figs. 1 and 2.—Two views of author's patient, Case 1.

The headaches occurred frequently until a few years before entrance. The weak spells caused her to fall down and when picked up she was limp "as a rag." There was no foaming at the mouth or biting of the tongue. At first the spells occurred once a week, but she had had none for three years. There was no vomiting.

Following this illness and until two years before entrance, she had involuntary defecation and incontinence of urine, but at the time of entrance she had no trouble in that respect. She has always had a good memory. She has always been constipated.

At present there is no headache, she has control of the sphincters. There are no convulsions or rigidities. She can walk and talk, but does not know whether or not the sun is shining.

Menstruation began at 13 years, regular monthly type, with a duration of four days. The flow was moderate in amount, and there was no dysmenorrhea or metrorrhagia.

The mother and father were well and never had been seriously ill. The maternal grandparents were well at 70 and 72. The paternal grandfather died of pneumonia, the grandmother of "old age."

There is no similar case in the family. The mother had thirteen live children, of which the patient was number ten. Four are dead: two of pneumonia at 8 and 16 weeks of age, one being the eighth child; one of diphtheria at 21 weeks, being the second child; one lived three or four days, an eight months' pregnancy; a full-term pregnancy, the ninth, resulted in a dead baby. Nine children are living, the other eight are very well. The oldest, a woman of 30, has one child who is well. She had a seven months' spontaneous miscarriage. There are no other daughters married. Two sons are married; their wives have never been pregnant. All the children walked and talked early. The mother denies any evidence of specific disease in herself or husband.

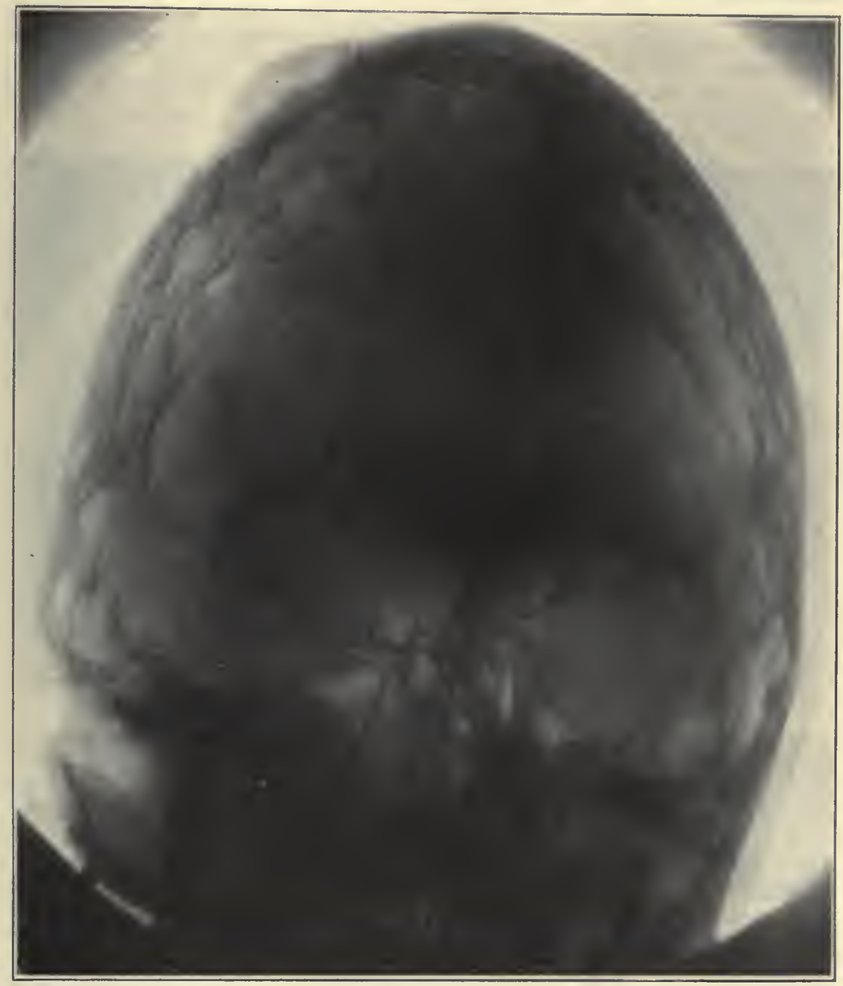

Fig. 3.—Roentgenogram of cranium, Case 1; anteroposterior view

Physical examination was made by Dr. Kanavel, Oct. 1, 1915. The patient proved to be a fairly well-nourished girl of normal size for fourteen years of age. There was rounded kyphosis in the upper portion of spine, with slight lordosis, probably postural in origin. The patient was in the habit of sitting with the mouth open and the lower jaw dropped. The lower lip was thick. When mouth was closed the lower jaw projected 1 cm. above the upper jaw. The nose was turned slightly to the right. There was marked exophthalmos of both eyes, especially the right. There was divergent strabismus when eyes were at rest. On the slightest tension there was marked double nystagmus.

There was marked anteroposterior nondevelopment and excessive vertical development of the cranium (Figs. 1, 2, 3 and 4). The protuberance along the median line was 7.5 cm. long and 5 cm. wide. On the anterolateral aspect of this protuberance a semifluctuant sensation could be elicited. This was a hernia cerebri and was tender (Fig. 3). Otherwise the body was symmetrical and there were no gross deformities.

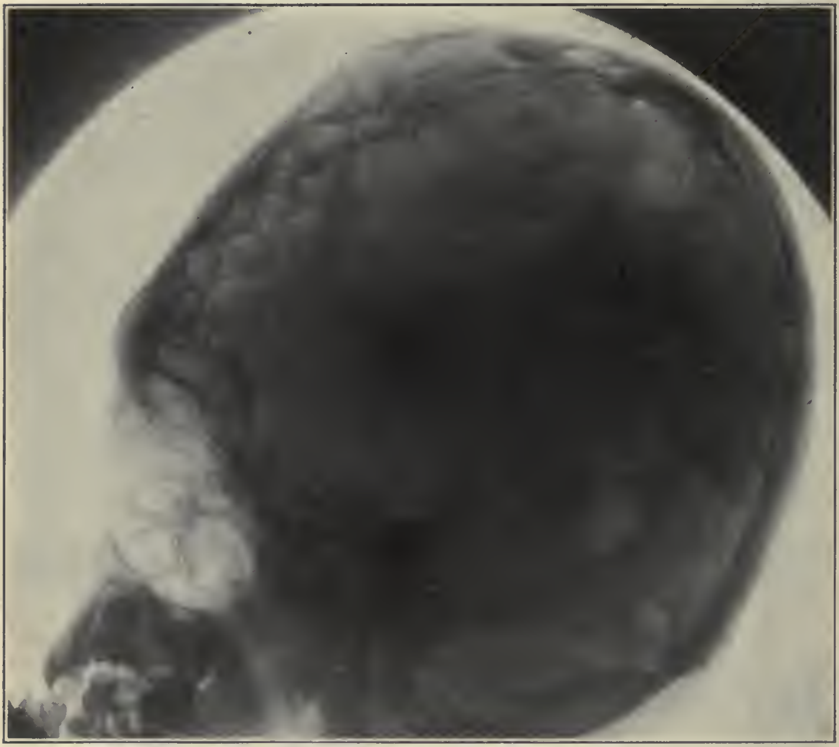

Fig. 4.—Lateral view of skull in Case 1, showing hernia cerebri.

Measurements taken showed the circumference of the head around the occipital protuberance and glabellum to be 48 cm.; the occipitoglabellum diameter over the vertex, 32 cm.; auditory meatus to auditory meatus (around the head). 66 cm.; and the mentooccipital diameter, 60 cm.

The child habitually protruded the tongue to the right, but showed no marked evidence of paralysis. She swallowed without difficulty. The facial nerve was intact. It was impossible to estimate accurately the power of the ocular muscles, but the patient did not turn the eyeballs inward. The eccentric pupil was at the upper inner quadrant of each eyeball.

Sensation over the body was normal. The muscular sense was normal except in the right arm. The knee reflexes were normal. There were no Babinski, Oppenheim, Gordon or ankle clonus. There was apparent loss of the stereognostic sense in the right hand.

The lungs and the heart were normal. The right arm was smaller and weaker than the left.

Examination of eyes by Dr. Patillo showed the pupils dilated, with no response to light. There was lateral nystagmus. Light perception was absent, due to a double primary optic atrophy.

Examination of the ears by Dr. J. Gordon Wilson revealed a chronic suppurative otitis media on the left side. There was no other gross pathology of the sphenoid bones.

Temperature ranged from 97.6 to 98.6, the pulse from 76 to 104, usually about 90. The respirations varied from 18 to 24.

Blood examination, made Sept. 27, 1915, showed 4,952,000 red blood cells, 15,800 white blood cells, lymphocytes 22 per cent., large mononuclears and transitionals 5 per cent., polymorphonuclear neutrophils 72 per cent., polymorphonuclear basophils 1 per cent., hemoglobin 98 per cent. (Dare). On September 29 blood examination gave 5,656,000 red blood cells, 14,000 white blood cells, lymphocytes 22 per cent., polymorphonuclears 78 per cent., hemoglobin from 91 to 94 per cent. (Dare).

Three examinations of the urine each proved negative. An examination of the spinal fluid was made Oct. 2, 1915. The Wassermann reaction performed by Dr. Holmes proved negative. Spinal fluid examination made by Dr. A. L. Moody on Mrs. S., the patient's mother, on the same date, showed Nonne and Noguchi reactions both negative. The cell count was 5 per c.mm. The Lange test was negative.

Case 2.—W. McC., a colored boy, aged 6 years, entered St. Luke's Hospital on the service of Dr. H. W. Cheney (later transferred to Drs. F. X. Walls and J. Brennemann). The complaint, as given by the mother, was stiffness of neck, headache, bulging eyes and lateral retraction of the head. Two months before admission the boy began to have attacks of stiffness in the side and back of the neck. These attacks lasted from 1 p. m. till bedtime and were unilateral, but involved both sides at different times. Simultaneously his head began to lean toward the right. His trouble was exaggerated by "colds."

Previously he had been like the other children, but when these attacks began he acted "dopey." He had fever almost every afternoon. Headache usually began at 11 a. m. and continued until bedtime. The appetite was unaffected.

The eyes began to bulge when the boy was 5 or 6 months old, but his vision was apparently unaffected. The shape of his head had been unusual from birth. The date of closure of the anterior fontanel was unknown. The boy was a mouth breather. He was taken out of school because of headaches, which were promptly alleviated. The boy had measles at 4 years and mumps at 5, but no other illness.

He had a sister who at 6 years of age started to have similar trouble, that is, stiffness of the neck with retraction of the head. She died of tubercular meningitis three months later. There are two other sisters, one well, the other, 14 years old, has been in the Municipal Tuberculosis Sanitarium for two months. She has tubercular cervical adenitis. The father died of pulmonary tuberculosis six years before. The mother was in good health.

The patient was a negro boy about 6 years of age. The development and nutrition were good. There was no marked evidence of rickets and no rash. The head was large, of the typical shape of acrocephaly. It came up to a point like a dome (Figs. 5 and 6). The scalp was negative. The fontanels were closed. Measurement showed the diameters to be as follows: suboccipitobregma 15 cm., suboccipitofrontal 17 cm., occipitofrontal 17.5 cm., occipitomental 22 cm., biparietal 12.5 cm., bisacromial 25 cm. The circumferences were as follows: Occipitofrontal 50.5 cm., suboccipitofrontal 50 cm., bisacromial 74 cm. The distance between the external auditory meati over the dome was 36 cm.; from the inion to the nasion over the dome 36 cm. From the external auditory meatus to the highest point of the skull the distance was 17.5 cm. The circumference from the chin to the subocciput was 47 cm.

The head was drawn to the right. There was marked exophthalmos. When the boy closed his eyes the sclera was exposed for a space one-eighth of an inch wide. This was more marked on the right side. The ears and nose were normal, the throat hyperemic, the teeth good, palate very highly arched. The neck was not rigid. The cervical glands were shotty.

There was a slight rosary, but the heart and lungs were normal. The abdomen was large (pot-belly) but there was no tenderness, rigidity, or enlargement of the viscera. The extremities showed slight evidence of rickets. The reflexes were exaggerated.

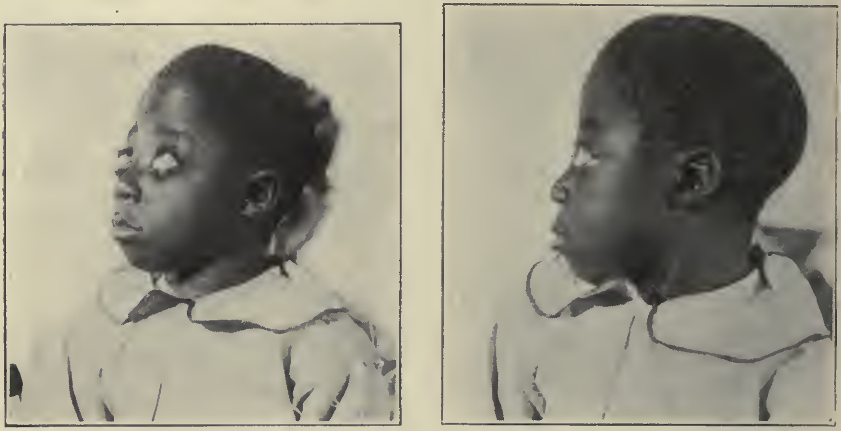

Figure 5 Figure 6

Figs. 5 and 6.—Two photographs of colored boy, author's Case 2, as described in text.

On Jan. 6, 1916, examination of the eyes was made by Dr. Brawley. The primary optic atrophy was not far advanced and the vessels had not as yet shrunken. The disk was white and vertically oval; with the ophthalmoscope the disk was best seen, left eye with + 3, right eye with + 4.

The urine was negative; the white blood cells 14,800. A roentgenogram made by Dr. C. L. Moir, Dec. 24, 1915, showed a marked case of acrocephaly (Fig. 7). Dec. 21, 1915, the Wassermann reaction was negative, performed by Dr. Leila Jackson. The highest temperature was 100.4. The patient runs a slight afternoon fever of about 99.4. There are no night sweats or cough. The appetite is good. The report of Mrs. Bersch, kindergarten teacher, shows that the mentality is good. He can be taught as easily as other children of his age and race.

Because of failure of the lids completely to cover the eyes the boy developed an orbital conjunctivitis. While that part of the treatment consisting of boric solution irrigation was being done, on one occasion the eyeball became dislocated from simply inverting the lid. It was replaced with little difficulty.

The diagnosis in a well-developed case of acrecephaly is easy. A good history is of value. Physical examination, with careful ophthalmoscopic study, is usually conclusive, and the Roentgen ray will clear up any doubtful cases. The prognosis as to life is good, as to improvement very poor.

There is no satisfactory treatment. In 1913 Schlosser[14] reported to the German Surgical Congress his operation on two patients. It consists in turning down a skin and bony flap on the forehead, then the dura and frontal lobe are lifted up and the superior portion of the optic canal is removed with a chisel. He performed the operation on two children with practically no visual improvement whatever. Treatment with glands of internal secretion has been suggested, but there are no data on the subject.

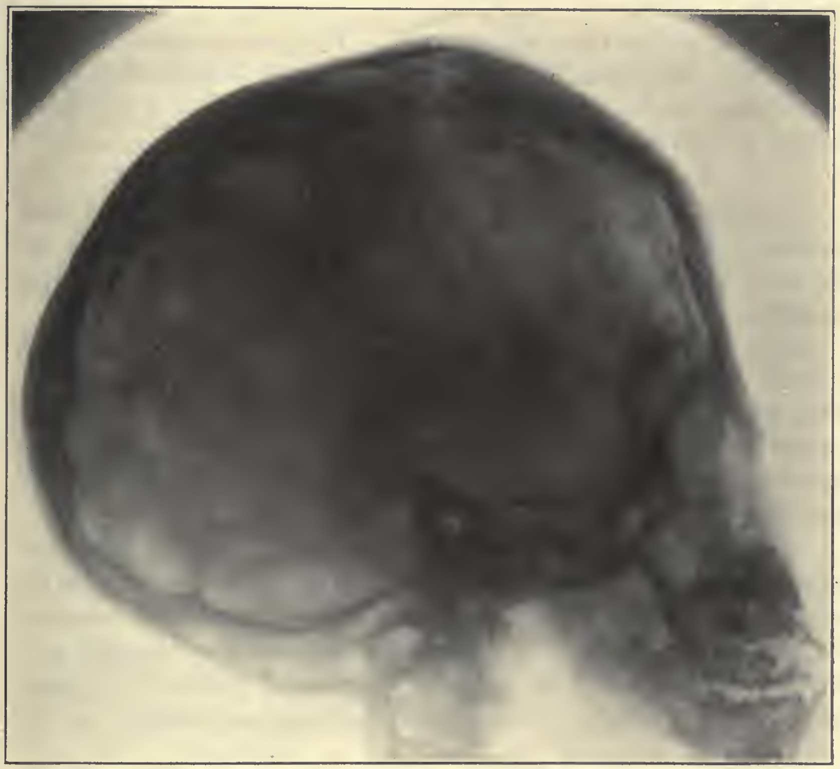

Fig. 7.—Roentgenogram of head, author's Case 2; lateral view.

Gadelius[13] and Davis[15] report excellent cases of acrocephalosyndactylism. The former shows photographs and roentgenograms of cases. One patient had fusion of first three fingers of both hands; another had no thumbs and the fingers were fused into one mass with practicaly total absence of metacarpals; another had thumbs, but the fingers were fused into one mass. The foot had a similar deformity.

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[14] Schlosser: Deutsche Gesellschaft für Chirurgie, Germ. Surg. Cong., 1913; Arch. f. Ophth., 1904, **58,** 151, A673.

[15] Davis, Ben: Am. Jour. Dis. Child., 1915, **9,** 446.

Stein[16] reported an interesting case with mentality and fundi unaffected, but with typical dimpling of the inner table of the skull. The condition was unknown to the patient. She sought advice for palpatation, dyspnea, cough and headaches, all of which were accounted for by a mitral stenosis.

Fenton's patient was 40 years old. He was a typical case of acrocephaly. His mentality was normal, in spite of an extreme deformity and the severest ocular complications. He suffered a traumatic rupture of both eyes.

SUMMARY

In summarizing I desire to say that these cases are probably more common than is generally believed. The diagnosis is very easy when one has a good history, makes careful physical examination, including ophthalmoscopic study, and has good roentgenograms.

Before we can have a rational treatment we must first establish a fairly definite etiology. To ascribe the condition to premature ossification of certain sutures sounds well, but what causes the sutures to ossify prematurely? Is acrocephaly a syndrome due to some disturbance of one gland of internal secretion, or is it a pluriglandular syndrome?

It seems reasonable that the treatment should proceed along one or two lines, namely, first gland, or extracts of glands, of internal secretion, second, when symptoms of intra-ocular pressure or optic compression are found, if a skilled decompression is performed, with removal, either partially or totally, of the superior portion of the optic canal, some hope might be offered these unfortunate patients.

In conclusion I wish to express my appreciation of the kindness of Drs. Kanavel, Cheney, Walls, and Brennemann in permitting me to report these cases, and to those whose names are mentioned in the paper, my sincere thanks.

30 North Michigan Avenue.

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THE EXCRETION OF SODIUM CHLORID SOLUTION , INJECTED SUBCUTANEOUSLY *

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Hypodermoclysis as a means of replacing the loss of fluid which occurs in severe diarrhea, protracted vomiting or as a result of hemorrhage has been employed for a number of years with an increasing appreciation of its value in these conditions. Our studies of diarrheal stools showed great loss of salts, especially the more soluble ones, sustained in these intestinal conditions. It seemed to us, therefore, that benefit should result from the restitution not only of the water lost, but also of some of the salts themselves. The nature of the variations in weight after hypodermoclysis suggested that these were due to something more than simply a retention of the water injected. Moreover, in view of the necessity in many cases of repeating the injections, it was desirable to know exactly what the salt retention was. The observations which are included in this paper were undertaken to determine if any of the salt so given was retained, or how rapidly it was eliminated.

The solution employed was made from freshly distilled water and sterilized in the hypodermoclysis flask. This is an ordinary small-necked flask of about 250 c.c. capacity, fitted with a two-hole rubber stopper carrying short pieces of glass tubing, one of which is connected by rubber tubing with an ordinary hypodermic needle. The bottle containing the solution, heated to body temperature, is fastened, inverted, near the bed at a suitable height and kept sufficiently warm by being wrapped in a cloth. The needle is usually inserted in the back, preferably between the scapulae, and held in place by strips of adhesive plaster. The entire apparatus as well as the solution is sterilized and the injection is made with aseptic precautions.

Generally a physiologic salt solution was used; but in several instances a special solution, one suggested by Dr. Jacques Loeb, was employed as more nearly approximating the salt content of the blood than does a normal saline. The composition of this solution was sodium chlorid 0.86 gm., potassium chlorid 0.02 gm., calcium chlorid

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0.64 gm. (including water of crystallization), and distilled water 100 c.c.

In the cases here reported about 200 c.c. of the solution was allowed to run into the tissues. This usually required from one to three hours according to the degree of dehydration of the body of the infant, those most dehydrated taking up the solution most readily. Also, the first injections were taken up more rapidly than those given on succeeding days. The rate of absorption varied greatly, the time required for complete disappearance of the fluid from the site of injection ranging from four to twelve hours. The rate was slower in subsequent than in first injections.

Careful temperature records after injection were kept by Dr. C. B. Crawford of the resident staff in a large series of cases. A slight febrile reaction occurred in about one-fourth the children, even when the strictest precautions in preparing the solution were observed. The average temperature was about 101.5 F., though occasionally in susceptible infants temperatures as high as 103 were recorded. The rise of temperature commenced four or five hours after the beginning of the injection and continued on an average for six hours.

Whether the injection of the solution affects the volume of the urine and the number and character of the stools is a question regarding which there has been very little positive knowledge. Nor have many observations been made on the elimination of the salts after hypodermoclysis.

The literature of the last ten years contains numerous contributions on sodium chlorid metabolism. The point which has received most attention is the influence of salt on the body temperature. Besides this there have been a number of studies on the effect of the salt intake on the body weight. Several papers have discussed the difference in the effect of salt given by mouth and that given by hypodermic injection. A number of metabolism studies have been made on adults after salt injections, but we have been able to find only a single paper which gives metabolism figures in infants after salt injections.

Friberger[1] reports on five infants (four of whom were healthy) who received from 60 to 80 c.c. of a normal salt solution hypodermically. He found some increase in the salt excretion on the first day; the maximum excretion, the second day, and an excessive excretion continuing for two or three days longer. These observations, as far as they go, agree with our findings; but the number of cases is small, the amount injected was much less than in the cases reported here, and all of his observations, with but one exception, were on healthy children.

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[1] Friberger: A Study of So-Called Salt Fever and Chlorin Excretion in Infants, Arch. f. Kinderh., 1910, **53,** 17.

The series of investigations here reported was made with the view of determining the effect of hypodermoclysis on salt metabolism, and as far as possible on water metabolism in infants. For the last three years hypodermoclysis has been in daily use at the Babies' Hospital in a wide variety of conditions and has been given to many hundreds of children. Out of this number, twenty-four have been selected for special study. Of these, nine represent the type for whom hypodermoclysis is most frequently employed therapeutically; while fifteen, who may be considered normal children, were studied as controls. The age, food and general condition of these children are given in Table 1.

In eleven of the children the special salt solution mentioned was used; in the others the ordinary physiologic salt solution. The use of the Loeb solution was discontinued, because no clinical difference or unusual variations in metabolism could be discovered with its use.

In every instance the child was placed in the metabolism bed and total twenty-four hours' urine and feces were collected for one or two days before the salt solution was injected, and as a rule for three days after the injection. It would doubtless have been better to have had longer periods of observation, but it commonly happened that after five or six days conditions rendered it desirable to make changes in the treatment, thus necessitating comparatively short metabolism periods. It is also to be regretted that the intake by mouth unavoidably varied so much in some of the cases. It was the desire to make the observations under natural conditions and no attempt was made to force food when it was refused. The injection was always given at the beginning of a metabolism day.

In the first eleven cases complete metabolism studies were made of water, nitrogen, total ash, calcium oxid, magnesium oxid, phosphorus pentoxid, chlorin, potassium oxid and sodium oxid. In the remaining thirteen cases, however, only water and chlorin were determined. The separate determination of sodium oxid was omitted, being laborious and apparently of no importance for our purposes. If the sodium chlorid equivalent is desired it is obtained by multiplying the figure for chlorin by 1.648. In speaking of a water balance, it must be kept in mind that the water lost in the respiration and perspiration was not considered.

The methods used are the same as those reported in former papers from these laboratories.[2]

The only salt which could be expected to show a marked difference in the elimination after hypodermoclysis, even when the Loeb solution is used, is sodium chlorid, as this is the only one injected in any con-

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[2] Holt, Courtney and Fales: Chemical Composition of Diarrheal as Compared with Normal Stools in Infants. Am. Jour. Dis. Child., 1915, **9**, 213.

TABLE 1.—AGE, FOOD AND GENERAL CONDITION OF INFANTS USED IN INVESTIGATIONS OF EFFECT OF HYPODERMOCLYSIS ON SALT AND WATER METABOLISM

Name	Age,	Initial Weight, Gm.	Condition	Food	Stools
1. L. O....	10¼	5,285	Previously normal, but developing diarrhea	Protein milk	Watery and semiformed with fat-curds and mcus, yellow-brown and green
2. R. S....	12	7,143	Normal	Whole milk, 2 eggs, 1 oz. beef juice	Brown, soft, formed
3. H. R....	6	5,651	Normal, except for rickets	Fat 2.2, carbohydrate 6, protein 2, including dextrimaltose	Partly constipated, hard, brown; partly pasty, granular, with fat-curds and mucus
4 Jos. M...	17	10,305	Normal	Whole milk, 2 oz. cereal, 2 eggs	Pasty, semiformed with fat-curds and mucus, brownish yellow; later becoming watery and fermentative
5 Jos. S....	17½	9,615	Normal, after eczema	⅖ milk, ⅕ barley water, ⅖ water; 2 eggs; ½ oz. scraped beef	Thin, with mucus, yellow-brown
6. H. B....	13	6,998	Normal	Whole milk, cereal, bread, 12 c.c. malt soup extract	Partly formed, constipated, brown; partly pasty, granular with mucus and fat-curds, greenish brown
7. S. J.....	9	4,897	Normal, but developed diarrhea during period	Fat 2.4, sugar 3, Protein 2.2, from condensed milk; barley flour 45 c.c.; cane sugar 15 c.c.	Partly formed, partly pasty; later becoming fermentative, with curds
8. T. M....	13¼	7,749	Normal	Whole milk, 2 oz. cereal	Partly pasty; partly watery, with fat curds, greenish
9. J. T....	9	6,650	Normal, except for rickets	Fat 3, sugar 4, protein 2.8; barley flour 45 c.c.	Partly constipated; partly softer, semiformed; brown
10. J. M....	11	7,359	Convalescent from scurvy	Skimmed milk; orange juice	Partly formed; partly pasty and watery, with fat-curds; yellow and gray
11. W. C....	6	7,179	Normal	Fat 2.4, sugar 4, protein 2.2; ½ egg	Mostly formed; partly pasty, with mucus; yellow-brown and yellow

12. P. D., 1	3½	3,686	Convalescent from diarrhea and vomiting	Protein milk	Partly formed; partly watery, with fat-curds; greenish yellow and gray
13. P. D., 2	7½	4,761	Normal	Fat 2.8, sugar 4, protein 2.6; ¾ oz. malt soup extract; 75 c.c. uncooked barley flour	Soft, formed, brown
14. M. di G.	5¼	4,305	Normal	Fat 2, sugar 2.5 protein 1.8, from condensed milk; imperial granum 30 c.c.; cane sugar 15 c.c.	Partly pasty, partly watery, with fat-curds and mucus; pale yellowish green
15. P. M.	3½	3,670	Normal	Protein milk, 5 feedings; and 2 feedings, fat 1.6, sugar 5, protein 1.4; 30 c.c. imperial granum in protein	Partly formed, brown; partly pasty and watery, greenish
1. I. G.	2½	2,814	Losing weight	Fat 1.8, sugar 2.25, protein 1.6, from condensed milk; barley flour 30 c.c.; cane sugar 8 c.c.	Loose, pasty, fermentative, with curds and mucus, greenish yellow
2. E. K.	6	3,765	Vomiting and losing weight	Fat 1.2, sugar 4, protein 2.2	Hard, formed, smooth, gray; later becoming softer, semiformed
3. J. C.	3½	4,358	Diarrhea	Protein milk	Watery, with fat-curds and mucus, greenish yellow
4 T. M.	2¼	2,855	Marasmus with diarrhea	Protein milk, barley water	Very watery, fermentative, with fat-curds and mucus, yellowish green
5. V. V.	2¼	2,953	Vomiting and losing weight	Fat 1.6, sugar 5, protein 2.2	Partly pasty, partly watery; with fat-curds and mucus; greenish yellow
6. J. B.	4½	3,716	Marasmus with diarrhea	Protein milk; 30 c.c. dextrimaltose	Very watery, with fat-curds and mucus
7. L. M.	5	4,432	Diarrhea and vomiting	Protein milk	Watery, with curds and mucus, greenish yellow; later becoming pasty and gray
8 J. P.	8	6,778	Diarrhea and vomiting	Protein milk; albumin water	Watery, with fat-curds and mucus, yellowish green and brown
9. C. B.	2	2,759	Marasmus with diarrhea	Protein milk; barley water; breast milk	Very watery, with fat-curds and mucus, greenish

TABLE 2.—METABOLISM STUDIES OF WATER—

Name	Period	Water Balance, C.c.							Chlorin Bal., Gm.	
		Intake by Mouth	Injected	Total In-take	Urine	Feces	Total Excre-tion	Re-tained	Intake by Mouth	Injected
1. L. O.	Before injection (daily aver,)	1,231	.....	1,231	470	187	657	574	0.8773	......
	1st day after....	1,149	193	1,342	450	358	808	534	0.6199	1.351
2. R. S.	Before injection	921	.....	921	300	24	324	597	1.1726	......
	1st day after....	1,113	198	1,311	577	38	615	696	1.1808	1.1286
3. H. R.	Before injection	1,015	.....	1,015	620	13	633	382	0.7046	......
	1st day after....	1,131	212	1,343	700	63	763	580	0.7192	1.1872
	2d day after....	1,121	.....	1,121	795	39	834	287	0.7262	......
4 Jos. M.	Before injection	771	.....	771	255	65	320	451	1.7956	......
	1st day after...	400	230	630	410	72	482	148	0.925	2.852
	2d day after....	521	.....	521	385	268	653	—132	1.0802	......
5. Jos. S.	Before injection	625	.....	625	140	137	277	348	1.0203	......
	1st day after....	649	235	884	220	93	313	571	1.0678	1.2925
	2d day after....	695	.....	695	330	154	484	211	0.7807	......
6. H. B.	Before injection (daily aver,)	1,035	.....	1.035	660	50	710	325	1.6876	......
	1st day after....	980	160	1,140	720	99	819	321	1.6265	0.8840
	2d day after....	1,005	.....	1,005	478	73	551	454	1.6543	......
	3d day after....	1,010	.....	1,010	550	59	609	401	1.6598	......
7. S. J.	Before injection (daily aver,)	955	.....	955	305	81	386	569	0.835	......
	1st day after....	1,055	180	1,235	630	191	821	414	0.923	0.994
	2d day after....	1,105	.....	1,105	420	200	620	485	0.966	......
	3d day after....	1,130	.....	1,130	290	284	574	556	0.988	......
8. T. M.	Before injection	920	.....	920	175	194	369	551	1.3635	......
	1st day after....	845	209	1,054	305	170	475	579	1.2523	1.0805
	2d day after....	830	.....	830	380	149	529	301	1.2301	......
	3d day after....	970	.....	970	378	135	513	457	1.4375	......
9. J. T.	Before injection (daily aver,)	858	.....	858	248	36	284	574	0.628	......
	1st day after....	845	190	1,035	435	27	462	573	0.619	1.0377
	2d day after....	855	.....	855	500	29	529	326	0.625	......
	3d day after....	800	.....	800	480	28	508	292	0.586	......
10. J. M.	Before injection	952	.....	952	285	68	353	599	0.8480	......
	1st day after....	1,030	206	1,236	235	89	324	912	0.7920	1.5553
	2d day after....	1,123	.....	1,123	410	82	492	631	0.8949	......
	3d day after....	962	.....	962	400	75	475	487	0.8546	......
11. W. C.	Before injection	865	.....	865	630	76	706	159	0.5420	......
	1st day after....	1,065	215	1,280	700	0	700	580	0.5280	1.1610
	2d day after....	1,125	.....	1,125	830	48	878	247	0.4716	......
	3d day after....	1,130	.....	1,130	790	21	811	319	0.5744	......

Chlorin Balance, Gm.					Summary
Total Intake	Urine	Feces	Total Excretion	Retained	
0.8773	0.0086	0.4678	0.4764	0.4009	All injected chlorin and water were eliminated in 24 hours; the water mainly through the feces, the chlorin equally in urine and feces
1.9709	0.5175	1.0498	1.5673	0.4036	
1.1726	0.492	0.0117	0.5037	0.6689	More than the amount of injected chlorin was eliminated in 24 hours; not more than half the water; the increased excretion was practically all in the urine
2.3094	1.7577	0.0228	1.7805	0.5289	
0.7046	0.4464	0.0081	0.4545	0.2501	The elimination of injected water and chlorin was slightly greater in the second 24 hours than in the first; somewhat more than the amount of injected chlorin was lost in 48 hours, but only half the water. The increased chlorin excretion was mainly through the urine, the water in both urine and feces
1.9064	0.9932	0.0540	1.0472	0.8592	
0.7262	1.0922	0.0338	1.1260	—0.3998	
1.7956	1.3158	0.0939	1.4097	0.3859	The injected chlorin was eliminated largely through the urine, the greater part in the first 24 hours; the injected water also in the first 24 hours' urine and a large amount besides in the feces of the second 24 hours; much more than the amount of both water and chlorin injected lost in 48 hours
3.7770	2.7267	0.0272	2.7539	1.0231	
1.0802	1.8446	0.1898	2.0344	—0.9542	
1.0203	0.4928	0.2262	0.7190	0.3013	Nearly all the injected chlorin eliminated in the first 24 hours and greatly increased excretion for 36 hours longer (the period of observation); increased water elimination in the second 24 hours, but not all the injected water lost; the increased excretion was in the urine
2.3603	1.7795	0.1620	1.9415	0.4188	
0.7807	1.4100	0.0777	1.4877	—0.7070	
1.6876	1.6104	0.0256	1.6360	0.0516	All the injected water and chlorin eliminated, mainly in the urine of the first 24 hours, after which the excretion was greatly decreased from the normal; retention therefore increased
2.5105	2.5200	0.0552	2.5752	—0.0647	
1.6543	1.2650	0.0409	1.3059	0.3484	
1.6598	1.4410	0.0327	1.4737	0.1861	
0.835	0.5216	0.0451	0.5667	0.2683	All the injected water and chlorin eliminated in the first 24 hours, the water and most of the chlorin through the urine; further loss of both chlorin and water through the feces, but to an increasing diarrhea following hypodermoclysis; diarrhea possibly due to feeding of high carbohydrate
1.9170	1.4364	0.2480	1.6844	0.2326	
0.966	0.7182	0.2610	0.9792	—0.0132	
0.988	0.6560	0.3690	1.0250	—0.0370	
1.3635	0.6720	0.0287	0.7007	0.6628	Practically all the injected water and chlorin lost in the first 24 hours' urine; but increased excretion of both water and chlorin continued 48 hours longer, resulting in greatly reduced average daily retention; feces somewhat reduced in both water and chlorin
2.3328	1.6000	0.0190	1.6190	0.7138	
1.2301	1.3440	0.0167	1.3607	—0.1306	
1.4375	1.1760	0.0151	1.1911	0.2464	
0.628	0.4695	0.0267	0.4962	0.1318	All injected water eliminated in urine in the first 24 hours; but increased excretion continued during period of observation (three days); about half the injected chlorin eliminated in first 24 hours' urine; increased excretion continued through period of observation, but not quite all injected chlorin was lost in 72 hours
1.6567	1.0266	0.0164	1.0430	0.6137	
0.625	0.7000	0.0172	0.7172	—0.0922	
0.586	0.6000	0.0171	0.6171	—0.0311	
0.8480	0.4418	0.0140	0.4558	0.3922	No injected water eliminated; chlorin excreted in part the first day, the maximum amount on the third day; nearly all the increased excretion was through the urine, both water and chlorin in the feces being only slightly increased; part of the chlorin was retained at the end of the third day, though increased excretion was continued
2.3473	0.8037	0.0185	0.8222	1.5251	
0.8949	0.7134	0.0159	0.7293	0.1656	
0.8546	0.9000	0.0304	0.9304	—0.0758	
0.5420	0.3780	0.0685	0.4465	0.0955	No injected water eliminated during time of observation; feces decreased and urine not increased so much as the intake by mouth; more than the amount of injected chlorin was eliminated in three days, somewhat more on the second and third days than on the first; increased excretion entirely through the urine
1.6890	0.8536	0.0000	0.8536	0.8354	
0.4716	0.9482	0.0264	0.9746	—0.5030	
0.5744	0.9408	0.0086	0.9494	—0.3750	

TABLE 2.—Metabolism Studies of Water and—

Name	Period	Water Balance, C.c.							Chlorin Bal., Gm.	
		Intake by Mouth	Injected	Total In-take	Urine	Feces	Total Excre-tion	Re-tained	Intake by Mouth	Injected
12. P. D., 1........	Before injection	651	.....	651	400	70	470	181	0.4626	......
	1st day after....	806	196	1,002	405	37	442	560	0.5603	1.3720
	2d day after....	798	.....	798	400	90	490	308	0.4351	......
	3d day after....	811	.....	811	335	67	402	409	0.4805	......
13. P. D., 2........	Before injection (daily aver,)	1,101	.....	1,101	617	28	645	456	0.7280	......
	1st day after....	1,035	210	1,245	575	23	598	647	0.6940	1.1865
	2d day after....	1,006	.....	1,006	670	65	735	271	0.6940	......
	3d day after....	1,065	.....	1,065	675	43	718	347	0.7160	......
14. M. di G.	Before injection	895	.....	895	445	177	622	273	0.7151	......
	1st day after....	875	144	1,019	495	125	620	399	0.7000	0.7546
	2d day after.... (2d injection)	930	206	1,136	725	159	884	252	0.7430	1.0712
	3d day after....	965	.....	965	480	101	581	384	0.7710	......
	4th day after....	945	.....	945	390	148	538	407	0.7560	......
15. P. M.	Before injection (daily aver,)	807	.. ..	807	535	25	560	247	0.5420	......
	1st day after....	920	100	1,020	515	24	539	481	0.5199	0.700
	2d day after.... (2d injection)	804	200	1,004	700	30	730	274	0.4861	1.420
	3d day after....	902	.....	902	520	16	536	366	0.4231	......
	4th day after....	938	.....	938	530	25	555	383	0.5489	......

siderable amount. It is, therefore, to this and to the water that the attention was especially directed.

As already stated, with eleven of the children complete metabolism studies, both before and after injection, were made of calcium oxid, magnesium oxid, phosphorus pentoxid and potassium oxid, as well as of sodium oxid and chlorin; but except as regards sodium oxid and chlorin, the differences between the retention before and after hypodermoclysis were no greater than the variations ordinarily observed when no injection of salt has been given. Moreover, there was no uniformity in the elimination of calcium oxid, magnesium oxid, phosphorus pentoxid and potassium oxid after the injections; sometimes the retention was practically unchanged, at other times there was a slight increase in retention, and in still others a slight decrease. In view of the indefinite character of the results of this part of the observations, the tables for these constituents have not been included in this report.

—Chlorin in Normal Children—(*Continued*)

Chlorin Balance, Gm.					Summary
Total Intake	Urine	Feces	Total Excretion	Retained	
0.4626	0.0720	0.1634	0.2354	0.2272	No injected water eliminated during period of observation (three days); less than half the injected chlorin lost through the urine on the first day and successively smaller amounts on the second and third days; a large part of the injected chlorin retained at the end of the period of observation
1.9323	0.7047	0.0543	0.7590	1.1733	
0.4351	0.3600	0.1218	0.4818	—0.0467	
0.4805	0.2211	0.1463	0.3674	0.1131	
0.7280	0.555	0.0164	0.5714	0.1566	All of the injected water eliminated on the second and third days, chiefly through the urine; about half the injected chlorin excreted in the first day's urine and a smaller amount on the second day, with normal excretion on the third day, leaving a part not eliminated
1.8805	1.0439	0.0074	1.0513	0.8292	
0.6940	0.8945	0.0209	0.9154	—0.2214	
0.7160	0.5902	0.0141	0.6043	0.1117	
0.7151	0.3827	0.0567	0.4394	0.2757	Very little of the injected water lost on the first day; on the following day, after a second injection, there was excreted through the urine an amount equal to the second injection; on the third and fourth days excretion through both urine and feces was so reduced that in the period of observation an additional amount of water was retained about equal to the two injections. All the injected chlorin was eliminated, mostly through the urine, in the first three days, the largest amount on the second day; on the fourth day there was normal excretion in the urine, but increased chlorin in the feces
1.4546	0.8800	0.0861	0.9661	0.4885	
1.8142	1.4210	0.1093	1.5303	0.2839	
0.7710	0.6048	0.1113	0.7161	0.0549	
0.7560	0.3520	0.1641	0.5161	0.2399	
0.5420	0.3373	0.0197	0.3570	0.1850	No injected water was lost on the first day; on the following day, after a second injection, there was excreted through the urine an amount about equal to the second injection, but on the third and fourth days, excretion was so reduced that in the period of observation an additional amount was retained more than equal to the two injections. A small part of the injected chlorin was excreted through the urine on the first day, a much larger amount on the second day; on the third and fourth days excretion was little more than normal, so that in the period of observation a considerable part of the injected chlorin was retained
1.2199	0.5305	0.0243	0.5548	0.6651	
1.9061	1.3020	0.0337	1.3357	0.5704	
0.4231	0.3172	0.0354	0.3526	0.0705	
0.5489	0.4664	0.0233	0.4897	0.0592	

Tables 2 and 3 give the results of metabolism studies of water and chlorin in normal and abnormal children. The accompanying illustrations (Figs. 1 and 2) represent graphically some of the fairly typical cases.

Among the fifteen normal children, seven eliminated all the injected water during the period of observation — six in the first day and one in three days; five excreted a considerable part during the period of observation, that is, two or four days; and three lost none in three days. Of the injected chlorin, ten children lost the entire amount during the period of observation—six on the first day, two in two days and two in three days; five excreted part of the chlorin in the period of observation—three days or four days. In four cases the water loss and in five the chlorin loss for the whole period was considerably more than the amount injected. In three cases the water loss and in one the chlorin loss was made up for by a subsequent decreased excretion, which caused an abnormal retention.

TABLE 3.—METABOLISM STUDIES OF WATER—

Name	Period	Water Balance, C.c.							Chlorin Bal., Gm.	
		Intake by Mouth	Injected	Total In-take	Urine	Feces	Total Excre-tion	Re-tained	Intake by Mouth	Injected
1. I. G.	Before injection (daily aver,)	725	.....	725	273	115	388	337	0.5467	......
	1st day after....	805	210	1,015	285	205	490	525	0.6070	1.160
	2d day after....	825	.....	825	450	101	551	274	0.6221	......
2. E. K.	Before injection (daily aver,)	603	.....	603	383	15	398	205	0.3260	......
	1st day after....	710	210	920	570	25	595	325	0.3840	1.1598
	2d day after....	730	.....	730	390	65	455	275	0.3950	......
	3d day after....	785	.....	785	450	47	497	288	0.4240	......
3. J. C.	Before injection (daily aver,)	553	.....	553	113	195	308	245	0.3526	......
	1st day after....	595	220	815	163	216	379	436	0.2654	1.650
	2d day after....	679	.....	679	140	234	374	305	0.4805	......
	3d day after....	553	.....	553	160	220	380	173	0.4002	......
4. T. M.	Before injection (daily aver,)	828	.....	828	278	303	581	247	0.5887	......
	1st day after....	1,067	208	1,275	830	199	1,029	246	2.5909	0.520
	2d day after.... (2d injection)	660	160	820	450	98	548	272	0.2194	1.200
	3d day after.... (13½ hr. only)	540	.....	540	335	85	420	120	0.1659	......
5. V. V.	Before injection (daily aver,)	623	.....	623	393	31	424	199	0.3670	......
	1st day after....	620	210	830	320	85	405	425	0.3654	1.160
	2d day after....	625	.....	625	360	26	386	239	0.3684	......
	3d day after....	630	.....	630	260	27	287	343	0.3713	......
6. J. B.	Before injection	985	.....	985	393	262	655	330	0.8570	......
	1st day after....	885	205	1,090	450	200	650	440	0.7837	1.025
	2d day after....	1,095	.....	1,095	450	176	626	469	0.8953	......
	3d day after....	1,010	.....	1,010	600	257	857	153	0.6319	......
7. L. M.	Before injection	550	.....	550	93	133	226	324	0.4175	......
	1st day after....	535	180	715	105	166	271	444	0.4061	0.9936
	2d day after.... (attempt at 2d inj.)	530	30	560	100	202	302	258	0.4023	0.1218
	3d day after....	550	.....	550	190	101	291	259	0.4175	......
	4th day after....	545	.....	545	180	45	225	320	0.4137	......
8. J. P.	Before injection	384	.....	384	54	240	294	90	0.2565	......
	1st day after....	440	200	640	40	85	125	515	0.2536	0.8480
	2d day after.... (2d injection)	485	220	705	205	472	677	28	0.4560	1.2950
	3d day after.... (3d injection)	450	220	670	200	274	474	196	0.4230	1.100
	4th day after.... (4th injection)	570	225	795	250	411	661	134	0.5370	0.960
	5th day after....	165	.....	165	95	396	491	—326	0.1550	......
	6th day after....	185	.....	185	65	230	295	—110	0.1740	......
9. C. B.	Before injection (daily aver.)	543	.....	543	283	94	377	166	0.6142	......
	1st day after....	595	205	800	355	166	521	279	0.6757	1.1316
	2d day after.... (2d injection)	545	225	770	270	200	470	300	0.5757	1.1070
	3d day after....	620	.....	620	360	133	493	127	0.3334	......
	4th day after.... (3d injection)	530	220	750	275	124	399	351	0.2768	1.2540
	5th day after....	610	.....	610	395	91	486	124	0.3274	......
	6th day after....	645	.....	645	345	148	493	152	0.3418	......

Chlorin Balance, Gm.					Summary
Total Intake	Urine	Feces	Total Excretion	Retained	
0.5467	0.1840	0.1410	0.3250	0.2217	Less than half the water and chlorin injected eliminated in 48 hours; the water excreted in the urine, the chlorin in both urine and first day's feces
1.7670	0.4480	0.2118	0.6598	1.1072	
0.6221	0.5240	0.1044	0.6284	—0.0063	
0.3260	0.3734	0.0080	0.3814	—0.0554	Part of the injected water eliminated the first day, mainly in the urine; on the two following days excretion so reduced in relation to intake by mouth that more than the amount injected was retained; no injected chlorin eliminated during the period of observation
1.5438	0.4390	0.0195	0.4585	1.0853	
0.3950	0.2690	0.0512	0.3202	0.0748	
0.4240	0.4050	0.0374	0.4424	—0.0184	
0.3526	0.0093	0.5539	0.5632	—0.2106	A small part of both water and chlorin injected was eliminated, mainly through the feces, in the three days of observation; the urine excretion was very low throughout the period
1.9154	0.0360	0.6212	0.6572	1.2582	
0.4805	0.0180	0.7268	0.7448	—0.2643	
0.4002	0.0120	0.6720	0.6840	—0.2838	
0.5887	0.3660	0.0482	0.4142	0.1745	The injected water was mostly eliminated through the urine the first and second days, the water in the feces being greatly reduced; no injected chlorin eliminated; the somewhat increased chlorin excretion in both urine and feces removed only part of the large chlorin intake by mouth of the first day, due to a mistake in adding salt to the barley water
3.1109	0.5271	0.1089	0.6360	2.4749	
1.4194	0.6075	0.0889	0.6964	0.7230	
0.1659	0.1977	0.0933	0.2910	—0.1251	
0.3670	0.3062	0.0171	0.3233	0.0437	No injected water eliminated in the period of observation; all the injected chlorin excreted, mainly through the urine of the first and second days
1.5254	1.040	0.0763	1.1163	0.4091	
0.3684	0.6320	0.0230	0.6550	—0.2866	
0.3713	0.3960	0.0245	0.4205	—0.0492	
0.8570	0.2223	0.3788	0.6011	0.2559	Not all the injected water eliminated in the three days of observation; the increased excretion in the urine; practically all the injected chlorin eliminated in the urine of the first day and in the feces of the third day
1.8087	0.8235	0.3291	1.1526	0.6561	
0.8953	0.1260	0.3653	0.4913	0.4040	
0.6319	0.1080	0.7580	0.8660	—0.2341	
0.4175	0	0.2016	0.2016	0.2159	All the injected water eliminated, partly in the feces of the first and second days, and partly in the urine of the third and fourth days; about half the injected chlorin eliminated through the feces of the first and second days; no excretion of chlorin in the urine during the period of observation
1.3997	0	0.4878	0.4878	0.9119	
0.5241	0	0.5934	0.5934	—0.0693	
0.4175	0	0.2161	0.2161	0.2014	
0.4137	0	0.0951	0.0951	0.3186	
0.2565	0.0912	0.1141	0.2053	0.0512	All the water of the four successive injections eliminated through the urine and feces, beginning the second day; increased excretion was continuing on the sixth day; nearly all the injected chlorin eliminated through both urine and feces, the increased excretion beginning on the second day; with decreased intake by mouth, excretion through the urine decreased, returning to normal on the sixth day; that through the feces was still high on the fifth and sixth days
1.1016	0.0960	0.0474	0.1434	0.9582	
1.7510	0.7200	0.2646	0.9846	0.7664	
1.5230	0.8960	0.4750	1.3710	0.1520	
1.4970	0.8800	0.7110	1.5910	—0.0940	
0.1550	0.3440	0.6840	1.0280	—0.8730	
0.1740	0.0800	0.3970	0.4770	—0.3030	
0.6142	0.3840	0.1409	0.5249	0.0893	Less than half the injected water eliminated during the period of observation, practically all the increased excretion being in the feces, which were still greater than normal on the sixth day; the larger part of the injected chlorin was eliminated during the period of observation by a small daily increase in both urine and feces; excretion was nearly normal in the urine, slightly increased in the feces on the sixth day
1.8073	0.5920	0.3440	0.9360	0.8713	
1.6827	0.6000	0.4160	1.0160	0.6667	
0.3334	0.5920	0.2170	0.8090	—0.4756	
1.5308	0.5280	0.2020	0.7300	0.8008	
0.3274	0.5796	0.1470	0.7266	—0.3992	
0.3418	0.3400	0.2400	0.5800	—0.2382	

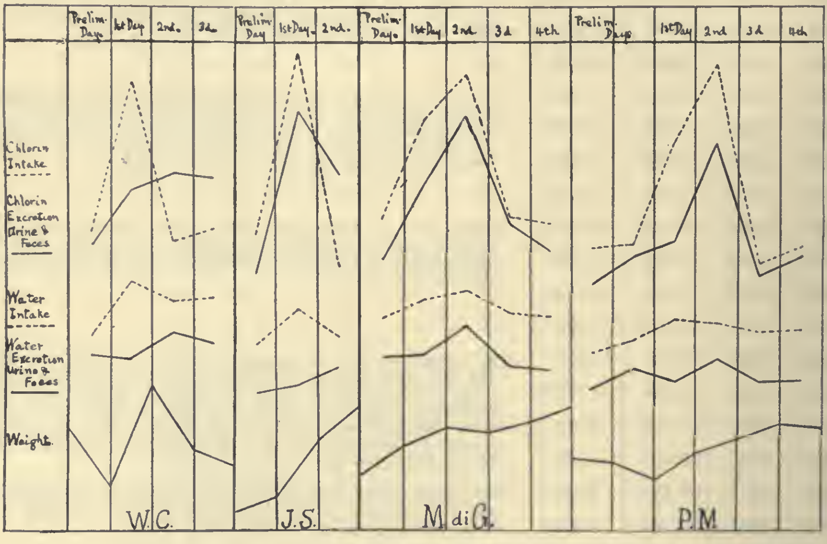

Fig. 1.—Chlorin and water intake and excretion in four normal children.

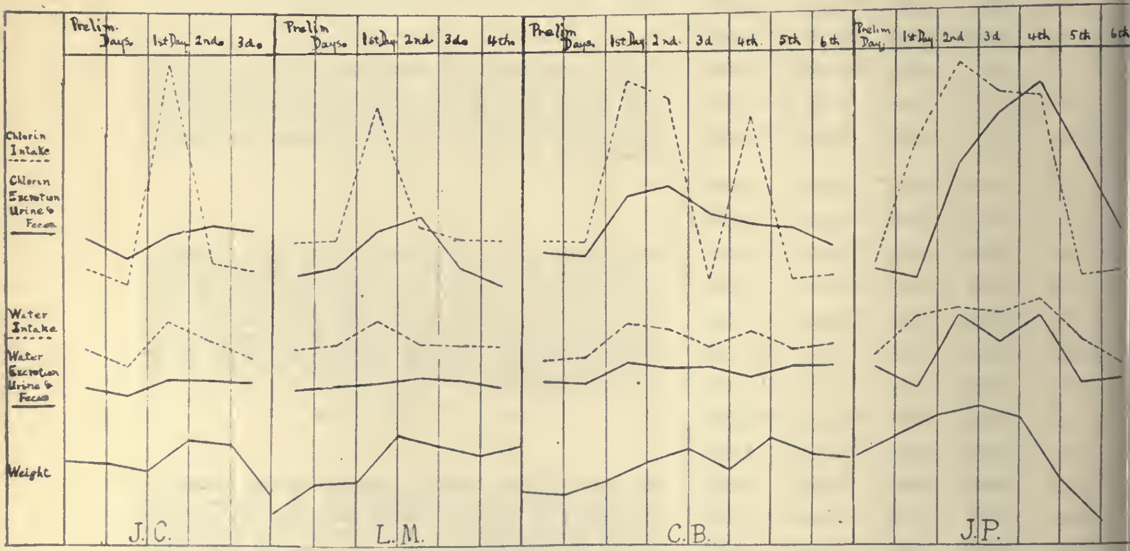

Fig. 2.—Chlorin and water intake and excretion in four abnormal children.

Among the nine abnormal children, only three lost all the injected water during the time of observation—one in the first day, one in four days and one in six days; four excreted part of the water in the period of observation—two, three or six days; two lost little or none in three days. Of the injected chlorin, one infant eliminated all in two days, one in three and one in six days; three excreted only part in the period of observation — two, four or six days; three lost practically none in the three days of observation. No excessive loss beyond the amount injected of either water or chlorin took place with any of the abnormal children. In one case there was an abnormal retention of water after the elimination of part of that injected.

TABLE 4.—Excretion of Water Injected in the Case of Twenty-Four Children

	Normal	Abnormal
All excreted in one day	6	1
Not entirely excreted in period of observation	8	6
Practically none excreted in period of observation	3	2

TABLE 5.—Excretion of Chlorin Injected in the Case of Twenty-Four Children

	Normal	Abnormal
All excreted in one day	6	0
Not entirely secreted in period of observation	5	6
Practically none excreted in period of observation	0	3

The loss of the water injected in the normal children took place in ten cases through the urine, in one mainly through the feces, and in one through both. The chlorin in fourteen cases was excreted through the urine; in one equally in the urine and feces. In one of the normal children, in whom diarrhea had developed shortly before the injection, excretion of the injected water took place wholly, and the chlorin partly, through the feces. The injected water and chlorin with the abnormal children was excreted mainly through the urine in two cases, through the feces in two, and about equally through both in three cases. With the children in whom elimination took place through the feces, diarrhea was always present before hypodermoclysis. In one normal child, to whom an unintentionally large amount of salt had been given, diarrhea developed on the second day, the injected water having already been eliminated in the urine.

The cases in which several injections were made on successive days merit special consideration. Two patients (C. B. and J. P., Table 3) received, respectively, three and four injections in four days. Both were suffering from diarrhea and both were very ill. The one with the most severe diarrhea (J. P.) excreted slightly more water than the amount injected, and nearly all the chlorin. The other (C. B.) retained a significant amount of both water and chlorin during the period of observation.

TABLE 6.—Sodium Chlorid Excretion in—

Period	R. S., Day Beginning 12 M.				H. R., Day Beginning 10 A. M.				J. M., Day Beginning 10:30 A. M.			
	Water, C.c.		Chlorin, Gm.		Water, C.c.		Chlorin, Gm.		Water, C.c.		Chlorin, Gm.	
	Intake*	Urine	Intake	Urine	Intake	Urine	Intake	Urine	Intake	Urine	Intake	Urine
1st day												
1	......	262	....	0.9777	......	135	....	0.2295	.....	160	......	0.7867
2	......	80	....	0.0992	......	210	....	0.2940	.....	90	......	0.7812
3	......	125	....	0.4113	......	165	....	0.2360	.....	90	......	0.6660
4	......	110	....	0.2695	......	190	....	0.2337	.....	70	......	0.4928
Total..	1,311	577	2.3094	1.7577	1,343	700	1.9064	0.9932	630	410	3.7770	2.7267
2d day												
1	......	.....	....	....	......	300	....	0.4230	.....	100	......	0.7080
2	......	.....	....	....	......	155	....	0.2403	.....	80	......	0.5920
3	......	.....	....	....	......	155	....	0.2356	.....	110	......	0.1342
4	......	.....	....	....	......	185	....	0.1933	.....	95	......	0.4104
Total..	......	.....	....	....	1,121	795	0.7262	1.0922	521	385	1.0802	1.8446
3d day												
1	......	.....	....	....	......	.....	....	....	.....	...	......	......
2	......	.....	....	....	......	.....	....	....	.....	...	......	......
3	......	.....	....	....	......	.....	....	....	.....	...	......	......
4	......	.....	....	....	......	.....	....	....	.....	...	......	......
Total..	......	.....	....	....	......	.....	....	....	.....	...	......	......

* The figures for the intake of water include the amount taken by injection.

The inference from these two cases seems warranted that repeated injections may be made without harm, and in some patients the water and salt is retained long enough to be of positive benefit. The increase in the diarrhea noted in the case of J. C. could hardly, under the conditions existing, be attributed to the injection. The beneficial effects of repeated injections in diarrheal cases have been abundantly confirmed by clinical observations.

Since in some cases the injected salt was entirely eliminated in the first twenty-four hours, it seemed desirable to collect the urine in shorter periods, in order to see how soon the increased excretion began. With six children, therefore, the collection of urine following hypodermoclysis was made in six-hour periods. The results are shown in Table 6.

A study of the water and chlorin excretion in this series showed a striking want of uniformity. This was true not only of the different children, but of the same child on different days. One child (R. S.) eliminated a very large part of his chlorin intake in the first six hours; very little in the second six hours; and again, quite large amounts in the third and fourth periods. H. R. and J. H. excreted almost uniform amounts in all the periods of the two days. The other three children were alike in eliminating little or none of the injected chlorin in the

—Six-Hour Periods Following Hypodermoclysis

J. S., Day Beginning 9:15 A. M.				W. O., Day Beginning 11:30 A. M.				P. D., Day Beginning 10 A. M.			
Water, C.c.		Chlorin, Gm.		Water, C.c.		Chlorin, Gm.		Water, C.c.		Chlorin, Gm.	
Intake	Urine	Intake	Urine	Intake	Urine	Intake	Urine	Intake	Urine	Intake	Urine
.....	40	......	0.1920	.....	140	......	0.1456	.....	65	......	0.1277
.....	70	......	0.6328	.....	195	......	0.2496	.....	170	......	0.3689
.....	75	......	0.6705	.....	155	......	0.2232	.....	210	......	0.3276
.....	35	......	0.2842	.....	210	......	0.2352	.....	130	......	0.2197
884	220	2.3603	1.7795	1,280	700	1.6890	0.8536	1,245	575	1.8805	1.0439
.....	20	......	0.1264	.....	240	......	0.1440	.....	190	......	0.1824
.....	225	......	0.8460	.....	205	......	0.1968	.....	80	......	0.0984
.....	60	......	0.3096	.....	155	......	0.3038	.....	235	......	0.3596
.....	25	......	0.1280	.....	230	......	0.3036	.....	165	......	0.2541
695	330	0.7807	1.4100	1,125	830	0.4716	0.9482	1,006	670	0.6940	0.8945
.....	130	......	0.6578	.....	190	......	0.1976	.....	205	......	0.1825
.....	70	......	0.3178	.....	190	......	0.1444	.....	40	......	0.0352
.....	...	......	......	.....	180	......	0.2952	.....	210	......	0.1701
.....	...	......	......	.....	230	......	0.3036	.....	220	......	0.2024
.....	...	......	......	1,130	790	0.5744	0.9408	1,065	675	0.7160	0.5902

first period, but differed greatly in the distribution of the excretion after that.

Again, there was no uniform relation of water excretion to that of chlorin. Although the excretion of the two frequently ran parallel, there were many instances in which the opposite was true. Among the individual factors influencing the manner of excretion of the hypodermoclysis solution, the rate of absorption is probably a very important one.

CONCLUSIONS

1. In acute diarrhea much salt and water are lost from the body. A similar condition is seen in marasmus, and after protracted vomiting, etc. When saline solutions are injected in such subjects a considerable amount of the salt is usually held for two or three days, and occasionally for a longer period.

2. If in these infants the variations in the loss of water by the skin and lungs can be ignored, the retention of water usually follows closely that of the salt.

3. Our metabolism studies support the clinical conclusions as to the beneficial effects of repeated saline injections in the conditions mentioned.

4. With normal children and with convalescents without evidence of dehydration, great variation is observed in the excretion of the injected water. It may be excreted very rapidly in the course of the first twenty-four hours, or part or all of it may be held for several days. The salt, however, is usually excreted rapidly, sometimes a large part of it in the first six hours.

THE FACTOR OF INANITION IN THE DEVELOPMENT OF ACETONURIA IN CHILDREN*

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Until very recently the terms acidosis and acetonuria have been used more or less as synonyms, but at the present time there is a tendency to use the term acidosis in a more general way and in a stricter chemical sense, as designating a condition in which there is a decreased alkaline reserve in the blood as a result of an overproduction or decreased elimination of acid bodies. We are interested in this paper only in that specific form or phase of acidosis which is distinguished from the others by the excessive formation of acetone, diacetic acid and beta-hydroxybutyric acid, or the so-called acetone bodies. It is a specific form of acidosis, in that faulty metabolism of the fats takes place, leading to the formation of these definite substances, while the other forms of acidosis are the result in many instances of very unclear processes.

Without entering on a detailed historical résumé we can briefly state the present condition of our knowledge in regard to these substances. For many years it has been known that acetone appeared in the urine of fasting individuals, after narcosis, in certain febrile and toxic conditions, and above all, in diabetes. Later it was shown that beta-hydroxybutyric acid was eliminated with the acetone and that it had the same origin, and further, that the extent of the acidosis could not be estimated from the acetone alone. However, it has only been in the last few years, as a result of the introduction of Shaffer's method, that the quantitative estimation of beta-hydroxybutyric acid has been satisfactory and feasible. For some time it has been a quite generally accepted view that the formation of the acetone bodies from the failure of proper metabolism of the fats is secondary to an insufficient utilization of carbohydrate. Magnus-Levy[1] makes the following statement:

> Formerly, numerous varieties of acetonuria were distinguished, such as those occurring in inanition, in fever, in infection and intoxication, in diseases of the stomach and intestine, in nervous and mental affections, etc. All the above-named forms of acetonuria can, however, be referred to the same and

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* From the Department of Pediatrics, Washington University Medical School, and the St. Louis Children's Journal.

[1] Magnus-Levy: v. Noorden's Metabolism and Practical Medicine, London, 1907, **1,** 171.

> identical cause, just as the acidosis of diabetes can, namely, the entire, or almost entire, deficiency of carbohydrates in the metabolism.

This summarizes very well what might be considered the generally accepted viewpoint.

As a result of the recent work of Allen[2] and other American workers in diabetes, however, there seems to be reason to question the correctness of this view. It has been shown that a diabetic acetonuria may be lessened by fasting and this has occurred in some cases when the dextrose-nitrogen ratio was approximately 3.6 to 1, or at a time when the body was almost entirely unable to oxidize sugar. Moreover, other chemists, as Taylor, hold a different view. Taylor[3] holds that certain clinical and experimental facts, as well as theoretical considerations, are opposed to this view of carbohydrate deficiency. For example, he considers the severe acidosis seen at times following narcosis as "not one associated with the carbohydrate metabolism; it is a result of the necrosis of the liver." Likewise, in other conditions, as cyclic vomiting, in which acetonuria occurs, Taylor does not believe that carbohydrate insufficiency is the cause of the acidosis.

The subject is of particular interest to the pediatrician, as despite the infrequency of diabetes at this age period, acetonuria is very common in childhood and its association with narcosis, cyclic vomiting, and many febrile and toxic conditions is often seen. In all of these clinical conditions there is the possibility that inanition may be a factor to a greater or less degree. But the actual rôle played by inanition is very uncertain, for, as stated above, persistent fasting in some cases of diabetes seems to decrease the degree of acidosis. We have been surprised at the paucity of actual studies of ketonuria and fasting. Our knowledge is practically all derived from observations on professional fasters, and although the earlier writers, as Brugsch, give figures, in the last study of this kind, that by Benedict[4] on the faster Levanzin in Boston in 1912, the chemical methods used were so defective that in a discussion of the acidosis the only conclusion reached was that "there was a material excretion of beta-oxybutyric acid."

As a part of a general study of acetone body acidosis in childhood, it has seemed essential to obtain figures of the degree of acetonuria resulting from inanition. So far as we know no figures exist on this point. Not only is this essential before acetonuria accompanying pathologic conditions can be studied, but inanition is so frequently used as a therapeutic measure in childhood that it is of interest to know how children react to the method of treatment.

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[2] Allen, F. M.: Jour. Am. Med. Assn., 1916, **66**, 1525.

[3] Taylor, A. E.: Digestion and Metabolism, Philadelphia, 1912, p. 358.

[4] Benedict: A Study of Prolonged Fasting, Publication of Carnegie Institute No. 203, 1915.

The method used for examination of the urine was that of Shaffer[5] in which the acetone and diacetic acid are distilled and determined by the iodimetric method of Messinger, and the beta-hydroxybutyric acid oxidized by potassium bichromate to acetone and determined in terms of the latter. Not all the acetone formed is excreted in the urine, but some uncertain and indefinite amount is eliminated through the lungs. To just what extent such elimination takes place is hard to determine. Some of the older papers give the impression that a large part may be eliminated in this way, but in a more recent study Folin and Denis[6] found that "the total acetone excretion with the breath in starvation is quantitatively insignificant." The method of calculating the expired acetone by analyzing small portions contains so many pitfalls, we decided the error would be less if this were left out of consideration and the amount of acetonuria used to express the degree of acidosis. The children used were on a standard metabolic diet previous to the experiments, in which from 40 to 50 per cent. of the total calories were in the form of carbohydrate. The general plan was to obtain a normal twenty-four hour excretion on this diet and then make determinations on twenty-four hour periods of inanition. The period of inanition varied in length as indicated below. At the close of the inanition the child was placed on the previous diet and twenty-four hour specimens were examined until a return to normal figures occurred.

The total quantity of acetone bodies in the urine during short inanition periods varies directly with the duration of the inanition. In five instances food was given at the end of twenty-four hours, and in the remainder the inanition period lasted forty-eight hours. The figures for the total quantity differed very widely, and hence we can best compare the results by expressing the degree of acetonuria in terms of kilograms of body weight. As might be expected, the total output in an infant is much less than in a child of 10 years. When on a complete diet the average amount of acetone bodies eliminated was about 0.003 gm. per kilogram of body weight (extremes from 0.001 to 0.007). In eight of eighteen cases studied the amount excreted in the first twenty-four hours was within these limits and averaged about 0.004 gm. In the remainder there was an increase, averaging about ten times the normal, or 0.030 gm. per kilogram. As a whole we can say that there is but little increased output of acetone bodies during a period of twenty-four hours inanition in a healthy child. In the cases (Cases 1, 2, 3, 6 and 12) in which inanition was terminated at the end of twenty-four hours, there was a continued increased elimination of acetone on the following day, which in some instances was greater than

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[5] Shaffer: Jour. Biol. Chem., 1913, **16,** 265.

[6] Folin and Denis: Jour. Biol. Chem., 1915, **21,** 183.

EFFECT OF INANITION ON ACETONURIA IN CHILDREN

Case No.	Condition as to Diet	Acetone and Diacetic Acid	Beta-hydroxy-butyric Acid	Total Acetone	Total Acetone per Kilo Body Wt.	Total Nitrogen	Ammonia Nitrogen	Per Cent. Ammonia Nitrogen	Remarks
1	Normal day...........	0.007	0.015	0.022	0.0037	1.739	0.173	10	Weight, 5.9 kg.; age, 3 mo. Fairly well nourished
	1st inanition...........	0.017	0.019	0.036	0.006	1.037	0.11	10.5	
	Return.................	0.029	0.042	0.071	0.012	1.712	0.198	11.5	
2	Normal day...........	0.01	0.007	0.017	0.0028	1.869	.....	....	Weight, 6.05 kg.; age, 8 mo. Good nutrition, but underweight
	1st inanition...........	0.086	0.157	0.243	0.04	1.709	0.365	21	
	Return.................	0.02	0.016	0.036	0.006	1.682	0.31	18	
3	Normal day...........	0.02	0.02	0.04	0.006	2.155	0.3	14	Weight, 6.48 kg.; age, 8 mo. Thin
	1st inanition...........	0.029	0.044	0.073	0.011	1.037	0.118	11	
	Return.................	0.039	0.025	0.064	0.01	1.154	0.141	12	
4	Normal day...........	0.01	0.014	0.024	0.002	1.667	0.125	7.5	Weight, 10.7 kg.; age, 10 mo. Well nourished; fat
	1st inanition...........	0.016	0.032	0.048	0.005	1.845	0.133	7.2	
	2d inanition...........	0.07	0.179	0.249	0.024	1.831	0.502	27	
	Return.................	0.04	0.088	0.128	0.012	1.93	0.487	25	
5	Normal day...........	0.037	0.012	0.049	0.004	2.525	0.245	9.8	Weight, 11.2 kg.; age, 18 mo. Fat; overnourished
	1st inanition...........	0.11	0.111	0.221	0.02	2.463	0.253	10.2	
	2d inanition...........	0.505	3.914	4.419	0.416	3.54	0.54	15	

6	Normal day...........	0.009	0.013	0.022	0.002	3.224	0.154	4.8	Weight, 12 kg.; age, 2 years. Well nourished
	1st inanition...........	0.052	0.128	0.18	0.015	2.777	0.143	5.2	
	2d inanition...........	0.126	0.474	0.599	0.05	4.348	0.4	9	
	Return.................	0.017	0.019	0.036	0.003	2.578	0.167	6.5	
7	Normal day...........	0.013	0.025	0.038	0.004	4.762	0.301	6.3	Weight, 8.7 kg.; age, 2 years. Poorly nourished; underweight
	1st inanition...........	0.15	0.447	0.627	0.072	3.295	0.191	5.8	
	2d inanition...........	0.315	1.041	1.356	0.159	3.462	0.562	16	
	Return.................	0.087	0.235	0.322	0.039	3.344	0.713	21.5	
	Normal.................	0.021	0.022	0.043	0.005	4.608	0.953	20.5	
	Normal.................	0.012	0.026	0.038	0.005	5	0.465	9.3	
8	Normal day...........	0.031	0.04	0.071	0.005	4.624	0.202	4.3	Weight, 13.5 kg.; age, 2 years. Fat; overnourished
	1st inanition...........	0.037	0.07	0.107	0.008	1.672	0.114	6.8	
	2d inanition...........	0.429	2.167	2.596	0.2	2.958	0.377	12.7	
9	Normal day...........	0.025	0.037	0.062	0.003	6.493	0.16	2.5	Weight, 24 kg.; age, 7 years. Somewhat undernourished.
	1st inanition...........	0.1	0.156	0.256	0.011	6.25	0.18	3	
	2d inanition...........	0.45	1.235	1.685	0.07	7.407	0.45	6	
	Return.................	0.132	0.373	0.505	0.021	10.929	0.578	5.2	
	Normal.................	0.011	0.023	0.034	0.001	6.896	0.338	5	
	Normai.................	0.018	0.031	0.049	0.002	7.038	0.362	5	

Effect of Inanition on Acetonuria in Children

Case No.	Condition as to Diet	Acetone and Diacetic Acid	Beta-hydroxy-butyric Acid	Total Acetone	Total Acetone per Kilo Body Wt.	Total Nitrogen	Ammonia Nitrogen	Per Cent. Ammonia Nitrogen	Remarks
10	Normal day............	0.012	0.045	0.057	0.003	8.205	0.356	4.3	Weight, 21 kg.; age, 7 years. Thin; undernourished
	1st inanition............	0.375	2.37	2.745	0.131	7.3	0.33	4.5	
	2d inanition............	0.765	3.044	3.809	0.18	7.425	0.785	10.5	
	Return..................	0.348	1.129	1.477	0.072	10.87	1.195	11	
11-1	Normal day............	0.01	0.075	0.085	0.002	9.259	0.497	5.3	Weight, 34.5 kg.; age, 11 years. Very well nourished
	1st inanition............	0.405	1.2	1.605	0.046	7.518	0.329	4.5	
	2d inanition............	0.846	2.745	3.591	0.104	7.143	0.792	11	
	Return..................	0.43	1.123	1.553	0.045	9.07	1.117	12.5	
11-2	Normal day............	0.013	0.029	0.042	0.001	7.055	0.194	2.7	Weight, 34.5 kg.; age, 11 years. Same as Case 11.
	1st inanition............	0.037	0.041	0.078	0.002	5.917	0.152	2.5	
	2d inanition............	0.92	3.435	4.355	0.127	8.18	0.41	5	
	Return..................	0.36	1.108	1.468	0.043	10.596	1.132	10.5	
12	Normal day............	0.03	0.07	0.1	0.004	13.745	0.438	3.2	Weight, 26.3 kg.; age, 11 years. Very thin and undernourished
	1st inanition............	0.112	0.324	0.436	0.016	7.752	0.327	4.2	
	2d inanition............	0.12	0.429	0.549	0.028	13.072	0.568	4.3	
13	Normal day............	0.015	0.113	0.128	0.004	10.526	0.404	3.8	Weight, 35.4 kg.; age, 10 years. Fat; overnourished
	1st inanition............	0.05	0.065	0.115	0.003	6.944	0.232	3.3	
	2d inanition............	0.315	0.705	1.02	0.029	9.231	0.465	5	
	Return..................	0.09	0.259	0.349	0.01	13.468	0.695	5	

14	Normal day...........	0.025	0.027	0.052	0.002	8.772	0.305	3.5	Weight, 24 kg.; age, 11 years. Thin; undernourished
	1st inanition...........	0.055	0.099	0.154	0.006	6.896	0.206	3	
	2d inanition...........	0.12	0.334	0.454	0.019	4.878	0.197	4	
15	Normal day...........	0.015	0.30	0.045	0.002	10.695	0.375	3.5	Weight, 25.4 kg.; age, 10 years. Thin; undernourished
	1st inanition...........	0.5	1.441	1.941	0.078	5.312	0.332	6.2	
	2d inanition...........	1.26	4.93	6.19	0.254	8.13	1.143	14	
	Return.................	0.5	1.094	1.594	0.066	11.204	1.242	11.1	
16	Normal day...........	0.008	0.004	0.012	0.003	0.568	0.168	29	Weight, 3.5 kg.; age, 3 mo. Fairly well nourished
	1st inanition...........	0.007	0.006	0.013	0.003	0.4	0.105	26	
	2d inanition...........	0.033	0.021	0.054	0.015	0.653	0.12	18	
	Return.................	0.016	0.013	0.029	0.008	0.615	0.082	13	
	Normal.................	0.008	0.009	0.017	0.005	0.358	0.075	20	
17	Normal day...........	0.01	0.013	0.023	0.003	3.96	0.158	4	Weight, 9.2 kg.; age, 17 mo. Fairly well nourished
	1st inanition...........	0.016	0.013	0.029	0.003	2.273			
	2d inanition...........	0.042	0.035	0.077	0.009	2.777	0.394	14.2	
	3d inanition...........	0.017	0.023	0.04	0.005	1.101	0.122	11	
	Return.................	0.037	0.038	0.075	0.009	3.472			
	Normal.................	0.023	0.032	0.055	0.006	2.747			
18	1st inanition...........	0.4	1.464	1.864	0.2	2.174	0.383	17	Weight, 9.3 kg.; age, 18 mo. Thin; undernourished. Post-operative
	2d inanition...........	0.925	3.312	4.237	0.455	4.255	0.99	23	

the amount eliminated on the day of the inanition. This fell rapidly, so that by the second day normal figures were again obtained.

In the remaining cases the inanition period was continued for a second twenty-four hours before the child was placed on the original diet. A rapid increase in acetone elimination took place during the second twenty-four hours. The most marked increase occurred in a well-nourished baby of 18 months (Case 5), in whom the acetone and diacetic acid jumped from 0.110 to 0.505 gm. and the beta-hydroxybutyric acid from 0.416 to 3.914 gm., or an increase from 0.02 to 0.416 gm. per kilogram of body weight. The greatest absolute amounts excreted were by a boy of 10 years (Case 15), who eliminated 1.26 gm. of acetone and 4.93 of beta-hydroxybutyric acid on the second day. The average amount excreted on the second day was about 0.15 gm. per kilogram of body weight.

On the day following two inanition days there was a continued acetonuria, but this was always less than the amount excreted on the second day of the inanition, contrary to what was at times found following one inanition day. On the second day following normal figures were obtained.

We have as yet very few data regarding pathologic conditions associated with acetonuria with which to compare these figures. Dr. Jeans is studying the acidosis of narcosis and we are investigating febrile and toxic conditions. The postoperative studies so far made do not show figures higher than these, and the figures from patients with pneumonia at its height and other febrile conditions are lower. In two cases of diabetes studied in our clinic which had a slight acidosis on diet, there was a decrease on a fasting day and an increase on the day following the fast, when a small amount of food was given. The figures did not exceed those obtained in these studies for inanition in healthy children.

In the discussion of the total acetonuria we have not considered the nutrition of the individual. There has been a rather widespread idea that the fat individual excretes more acetone bodies than the thin. This is perhaps the result of a paper by Brugsch[7] in 1905, in which he reported that a professional faster, who was in a fair condition of nutrition at the end of a prolonged fast, eliminated acetone bodies in the urine, while none were present in the urine of a patient with a stenosing carcinoma of the esophagus, who was so emaciated from starvation that there then was no longer any body fat present. Folin and Denis[6] have recently published the results of short fasts in two obese women and reached the conclusion that obesity is not a predisposing or contributing factor in the onset or intensity of the acidosis of starvation. As some of our children of the same age were fat and overnourished, and others thin and undernourished, they furnish some further confirmation of Folin and Denis' conclusion. For this comparison the total amount of acetone bodies for the two inanition days and the day following are added together. In Case 15, a poorly nourished lad of 11 years weighing 25 kg. excreted 9.725 gm., and an overnourished obese boy of 11 (Case 13), weighing 35 kg. excreted only 1.484 gm. in the three days. Another overnourished boy of 11, weighing 34 kg. (Case 11) excreted at one period 6.749 and at another 5.901 gm., or less than the undernourished boy. In some infants this same condition held; that is, there was no relation between the degree of acetonuria and the state of the child's nutrition. The children between whom these comparisons were made had all been on the same fixed diet before the period of inanition.

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[7] Brugsch: Ztschr. f. exper. Path. u. Therap., 1905, **1,** 419.

As was the observation with previous observers, we found that the amount of beta-hydroxybutyric acid (in terms of acetone) eliminated was as a rule from two to four times as much as the quantity of combined acetone and diacetic acid.

The nitrogen and ammonia of the urine was determined daily. There was at most a very slight actual increase or percentage increase in the ammonia elimination on the first day of inanition, and this in but a few cases. On the second day of inanition, however, a marked increased took place.

All of the children were closely watched for the development of clinical symptoms, particularly those which are so frequently regarded as signs of an acetone body acidosis in childhood. Not one child showed nausea, vomiting, flushing of the cheeks, temperature or hyperpnea. Except for some hunger in a few cases, not a child seemed to be affected in any way by the inanition. It seems hard to believe from our studies that the formation of acetone bodies per se, at least in the amounts produced by inanition, can be the fundamental cause of the symptoms so often regarded as due to acidosis.

The table contains the data for the different children studied.

INFANTILE SCURVY

IV. THE THERAPEUTIC VALUE OF YEAST AND OF WHEAT EMBRYO *

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Although we possess in orange juice a specific for infantile scurvy, it is well worth while to look about for other therapeutic agents which are potent in this disturbance. This is desirable from several points of view. In the first place, orange juice cannot be considered an ideal antiscorbutic food, as it is expensive and under certain circumstances difficult to procure, but more especially because it cannot well be embodied in the food. As a result of its having to be prepared and given separately, it is frequently forgotten by the physician or by the nurse, with the result that we encounter cases of latent or subacute scurvy which have come about through this oversight. Furthermore, as long as the true nature of the antiscorbutic vitamin is unknown, we shall gain valuable knowledge of the essential chemical substance which forms the basis of this disorder by ascertaining substances that do or do not possess antiscorbutic power. It was with these objects in view that yeast was resorted to in the prevention and cure of certain cases which have been reported in other connections. As is well known, yeast has been found to act as a specific in the prophylaxis and cure of beriberi, a disease which develops generally as the result of a diet of polished rice. In a previous paper[1] dealing with scurvy the intimate clinical relationship between these two deficiency diseases was pointed out, it being shown that in both there is involvement of the heart as well as of the central nervous system. Further observations have served only to strengthen our conviction of the group relationship between these two nutritional disorders. We hope to discuss in greater detail this clinical similarity at another time; however, it is evident that we might well expect that yeast would also prove of value in infantile scurvy. The diets of the infants on whom we wish to report consisted of preparations of pasteurized milk, with the addition of cereal in the case of those over 6 months of age. The milk was of excellent quality and had been pasteurized at 145 F. for thirty minutes. The only change which was made in the diet was the omission of orange juice, and the substitution of yeast in its stead, or in the case of very young

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* Read in abstract before the Society of Experimental Biology and Medicine, May 24, 1916, Proceedings, **13,** 145.

[1] Hess, A. F.: Jour. Am. Med. Assn., 1915, **65,** 1003.

infants who had not yet received orange juice, yeast was introduced into the dietary. The yeast was a fluid preparation, which was autolyzed and was prepared as follows: As soon as it was obtained from the brewery it was pressed to a consistency of putty, and was then allowed to autolyze in a thermostat for forty-eight hours. This fluid was of syrupy consistency, and as it contained considerable solid matter, composed mainly of the walls of the erupted yeast cells, it was diluted somewhat and filtered. It finally had a specific gravity of about 1.04. One or two tablespoonfuls of this fluid was added directly to the day's feeding of milk, or, in case the milk was not well taken, was given with a spoon.

The instances in which the yeast was given instead of orange juice to infants 6 months of age or under, in order to prevent the occurrence of scorbutic symptoms, are naturally the most interesting and significant, for it is evident that if it failed as a prophylactic, it could hardly prove to possess curative powers. We may summarize our experiences in this regard by the statement that our hopes of the efficacy of this therapeutic agent proved to be unfounded, as the young infants developed some signs of subacute or latent scurvy in spite of receiving the autolyzed yeast. The symptoms were not marked, and were promptly counteracted by the administration of orange juice; however, they were sufficiently definite to enable one to make a reliable diagnosis. The weight charts of two of these cases are appended (Charts 1 and 2), but must be regarded as unsatisfactory, as failure to gain in weight is but one sign of incipient scurvy, in some cases by no means the most significant one; in others, as pointed out elsewhere, it was entirely lacking. It will therefore be well to add a few details regarding these cases. The case portrayed in Chart 1 was that of a fairly well-nourished infant who had gained steadily until it was 5 months of age,

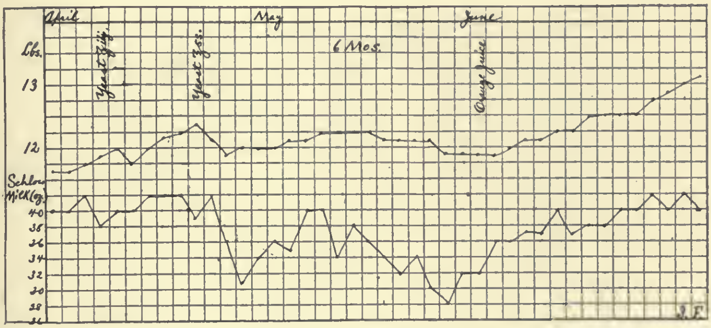

Chart 1.—Failure of yeast as a prophylactic; subacute scurvy promptly yielding to orange juice.

when it weighed about 11¼ pounds. It had been on Schloss milk[2] and had gained 3 pounds in the preceding two months. As it had hardly gained anything in the three weeks just elapsed, yeast was given in the beginning of April, as the chart indicated. In spite of the fact that yeast was continued for seven weeks, the baby's appetite became very poor (the yeast was then given by spoon), it failed to gain in weight and in May manifested tenderness of the lower end of the femur. All these signs and symptoms yielded promptly when orange juice was substituted for yeast.

The second case was that of a baby who had been admitted to the institution when 16 days old, weighing 6½ pounds. It was fed on Schloss milk and weighed 9½ pounds when 3 months of age. From this time, however, it failed to gain, so that it was considered a favorable case for prescribing yeast. As will be noted (Chart 2), yeast was given three weeks without effect. A change was then made to orange juice, with the remarkable result noted in the chart, namely, a prompt gain in weight, although the consumption of food remained the same. In addition there was an improvement in the general condition and a subsidence of eczema of the face, a phenomenon noted in two other cases following the administration of orange juice. We regard this as a case of latent scurvy in an exceptionally young infant.

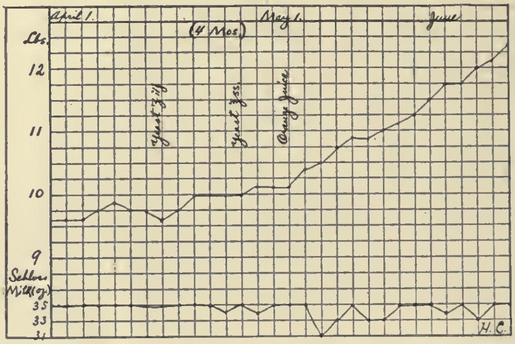

Chart 2.—Failure of yeast as a prophylactic; latent scurvy promptly yielding to orange juice.

The third case relates to a baby who entered the institution when almost 6 weeks old, weighing 4¾ pounds. It did well on Schloss milk, and weighed 7¼ pounds at 3 months, and 8¾ at 4 months, when yeast was added to the diet. About two weeks later its weight curve began to flatten. When 5 months old it contracted nasal diphtheria and its appetite was impaired. This infection yielded to antitoxin and the appetite improved. However, no gain in weight could be effected, even though cereal was added to the diet. The child was pale, had marked eczema of the neck and back, rapid respirations, tachycardia, and again loss of appetite. Orange juice was given, and all the symptoms abated, including the eczema and the cardiorespiratory disturbance.

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[2] Schloss milk is composed of 140 c.c. of milk, 140 c.c. of 20 per cent. cream, 35 gm. of dextrimaltose, 15 gm. of flour, 5 gm. of plasmon, 0.2 gm. of potassium chlorate and 700 c.c. of water. The milk and cream were pasteurized, and added to the other ingredients after they had been boiled for fifteen minutes and cooled.

In previous papers mention has been made of cases of mild scurvy developing on pasteurized milk. In two of these cases the autolyzed yeast was made use of to effect a cure. The one illustrated in Chart 3 is a case which was reported in detail in a recent paper treating of growth in scurvy[3] to illustrate the point that an infant who has been underfed may develop scurvy, notwithstanding a satisfactory gain in weight. When this baby showed scorbutic signs, much to our surprise, as it had seemed to be progressing well, we attempted a cure by means of yeast. This was given for eighteen days, in daily quantity of one half ounce and later one ounce. The peridental hemorrhages, the pallor, the lack of gain, the rapid respiration, nevertheless, persisted. The hope of accomplishing a cure by this means was then abandoned and orange juice was substituted for the yeast. This resulted in a prompt disappearance of the hemorrhages and a coincident improvement in all the symptoms.

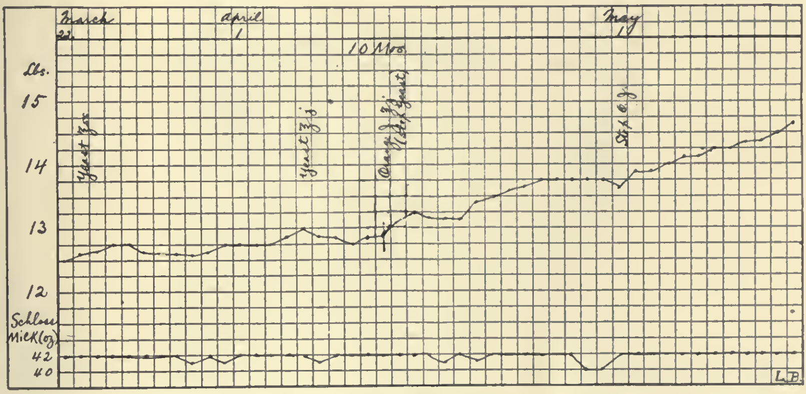

Chart 3.—Failure of yeast as a curative antiscorbutic.

As regards the other case in which yeast was employed as a curative agent, little need be added to what is illustrated in Chart 8. It will be seen that in this case, that of a well-nourished infant, both egg yolk[4] and germ meal water were tried before the autolyzed yeast. Under the yeast therapy the appetite decreased rather than improved, the general symptoms and the periosteal tenderness became more marked, so that after a trial of four days we resorted to orange juice. This brought about a decided improvement within from twenty-four to forty-eight hours.

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[3] Hess, A. F.: Am. Jour. Dis. Child., 1916, **12,** 152.

[4] According to McCollum and Davis egg contains both the fat and water soluble accessories for growth, Jour. Biol. Chem., November, 1915, **23,** 181.

It will thus be seen that yeast failed signally as an antiscorbutic from a prophylactic as well as from a curative point of view. If it possesses this property at all, it is in too slight a degree to be recognized clinically, and negligible from a practical and therapeutic point of view. Although this result was discouraging and not what had been anticipated, it shows conclusively that however close disorders such as beriberi and infantile scurvy may be, they must be regarded, in a clinical as well as in a chemical sense, as due to substances which are therapeutically totally different.

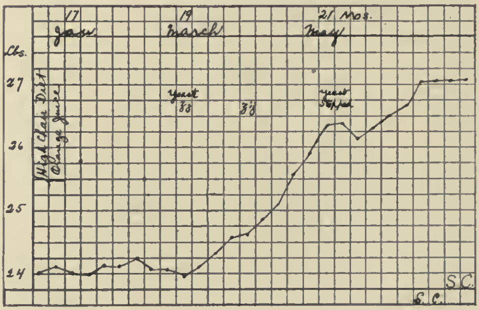

Chart 4.—Growth stimulated by means of autolyzed yeast in an older baby who had not gained for over two months.

Although yeast proved to possess little or no value as an antiscorbutic, it was found to be an excellent stimulant of growth. Thus the differentiation between an antiscorbutic and an essential growth stimulant—a distinction which was emphasized in the article in this series treating of growth in scurvy—was again substantiated. Following the addition of the yeast to the milk, there was in many instances a prompt rise in the weight curve. This sharp reaction led at first to the misconception that we were dealing with an excellent antiscorbutic substance. This inference was especially plausible in cases in which a gain was brought where none had taken place for weeks or months. But, as has been mentioned, the two phenomena were found to be by no means interdependent. In some instances infants gained 9 or 10 ounces the first week and then ceased to increase in weight; in others the gain was continued for several weeks. This favorable effect on growth was due, no doubt, in some cases to the stimulation of appetite, but in others there was a prompt response although the total intake of food remained the same. The yeast also had a favorable effect on the digestive processes, as shown not only by an increase of appetite, but by the character of the stools, which in some instances became normal where previously they had been constipated or poorly digested.

After it had been found that autolyzed yeast stimulated the growth of infants, it was determined to attempt to stimulate the growth of some older babies, who had maintained an almost constant weight for a period of weeks and months, in spite of various changes of diet. These children were from 1½ to 2 years old, and received a diet of milk, cereal, vegetables and fruit, which is termed "high chair diet" in the institution. In some instances cod liver oil had been given without avail. Yeast was now added to the diet, either in the autolyzed form or as yeast powder, which is prepared by drying the compressed brewer's yeast. One half ounce of the latter was added to the cereal or soup. It is unpalatable in whatever medium it is given, and although these children were successfully coaxed to take the prescribed amount, in many instances it was difficult to accomplish. Our results with these older infants were encouraging, as both the fluid and the dried yeast caused a definite gain in weight. This is well illustrated by Charts 4, 5, and 6, including two patients who received fluid yeast and one who was given the desiccated preparation.

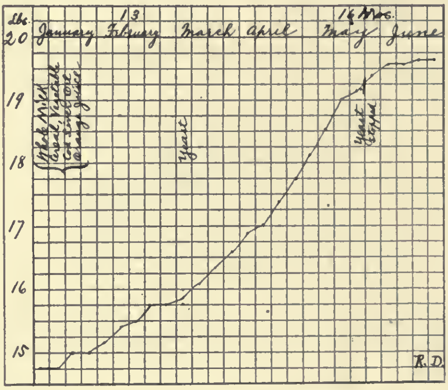

Chart 5.—Growth stimulated in an older baby by means of autolyzed yeast; gain of a pound in the two months previous to giving yeast, and of 2½ pounds in the subsequent two months.

In a previous paper treating more particularly of the relation of infantile scurvy and beriberi, mention was made of the use of wheat middlings as an antiscorbutic,[1] the subject being merely touched on and referred for detailed consideration to a later time. The wheat middlings were added to the wheat cereal (farina) in order to note its value as an antiscorbutic. In this connection a few words of explanation would seem in place. Farina is the starchy kernel of the wheat from which the outer layer has been removed. It has been repeatedly shown that beriberi is brought about by a diet of overmilled rice, which has been deprived of the outer layer or pericarp. It has likewise been established that the addition of rice polishings to the food suffices to effect a rapid cure of beriberi in man, or of its counterpart, polyneuritis, in birds. In view of these facts and the clinical similarity between infantile scurvy and beriberi, we decided to substitute in place of the farina a cereal containing the outer layer of the wheat. To this end we prepared a food consisting of two parts of middlings (the pericarp of the wheat) and one part of flour, and gave this in place of farina. No other change whatsoever was made in the diet. In some instances of scurvy improvement was noted; however, this could not be compared to the miraculous change brought about when orange juice was given. Frequently the gain in weight was not maintained, and in some cases there was not a concomitant improvement in the general symptoms characteristic of a mild form of scurvy. It seemed as if the middlings contained a small amount of the essential antiscorbutic substance, the vitamins of Funk, but a quantity insufficient to reestablish an adequate positive balance of this material. In view of the excellent results obtained by McCollum and his co-workers with the germ or embryo of wheat, it was determined to prepare a cereal containing this substance instead of middlings, to add this germ meal cereal to the dietary of pasteurized milk, and to observe whether it would not act as a substitute for orange juice. It will be remembered that McCollum and his co-workers found that they could produce marked growth in rats by adding wheat germ to the diet, and claimed that the germ contains two active accessory substances, one soluble in fat and the other soluble in water and stable to heat.[5] They also found that 8 per cent. wheat bran was no more efficient than 4 per cent. wheat embryo in promoting growth. More recently Sullivan and Voegtlin have reported the presence of an antineuritic substance in wheat bran, which may be obtained by means of hydrolysis and proper fractionization.[6]

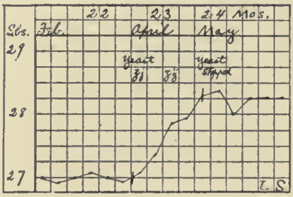

Chart 6.—Growth stimulated in an older baby by means of dried yeast; immobile weight for five weeks; gain of 1¼ pounds in the five weeks subsequent to giving yeast.

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[5] McCollum, E. V., and Davis, M.: Jour. Biol. Chem., November, 1915, **23,** 181.

[6] Sullivan, M. X., and Voegtlin, C.: Jour. Biol. Chem., March, 1916.

Wheat embryo is particularly rich in fats, the preparation which we employed containing 10.9 per cent. of ether-soluble extract. It was found that a cereal composed of equal parts of wheat germ and of farina was too rich for infants to take for long periods, and that they soon lost their appetites and refused it. If, however, only one third of the germ meal was used, this loss of appetite did not ensue. Accordingly, a cereal was made of this composition, was cooked for two hours, as had been the custom, and was given twice a day in as large amounts as the individual infant would take, some consuming as much as eight or ten tablespoonfuls a day. The results may be summarized by the statement that this food was incapable of replacing orange juice and could not be relied on to prevent the development of subacute scurvy. The case represented in Chart 7 is illustrative of this point. Here we note an infant that received the germ meal when it was 6 months old, and notwithstanding, showed definite signs of subacute scurvy, including tenderness and thickening of the lower end of the femur, three months later. This case is particularly interesting, as it illustrates the fact that an infant can gain in weight steadily while the scorbutic condition is slowly developing and advancing. In the last paper[3] an instance was cited, accompanied by a weight chart, of a baby previously underfed, who gained for weeks and months while developing scurvy. The present case shows that these apparently paradoxical phenomena may be concurrent in a well-nourished infant of normal weight who has received a sufficient quantity of food. Of the six infants placed on this cereal, three did satisfactorily, two showed some scorbutic signs, and a third appeared moderately well, but reacted later with a sharp gain in weight when orange juice was added to the diet, a reaction which we interpret as signifying that it had been receiving an insufficient amount of antiscorbutic foodstuff.

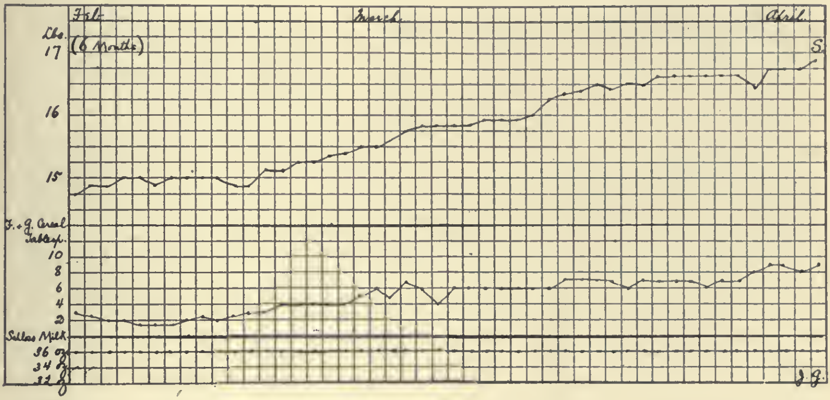

Chart 7.—Failure of wheat embryo as a prophylactic; development of subacute scurvy in a well-nourished infant despite gain in weight. (F. and G. cereal indicates farina and germ meal.)

On Chart 8 it will be observed that "germ meal water" is recorded. This is an extract prepared somewhat after the method of the barley water, which is so commonly used in infant feeding; one tablespoonful of wheat germ meal is added to a pint of water, allowed to soak for two hours, and then boiled for two hours. We obtain in this way the water soluble substance of the germ meal, which, according to McCollum, has a remarkable growth stimulating effect, and is responsible for the cure in polyneuritis.[7] It will be seen that in this case giving the extract of the germ in addition to the cereal failed either to improve the appetite or to bring about a gain in weight; it may be added that it also failed to relieve the typical scorbutic symptoms. In some infants the addition of this germ meal water to the diet effected a sharp gain in weight, which was not the case, however, when the failure to gain was part of a scorbutic condition. Under ordinary circumstances stationary weight is to be regarded as a general nutritional disturbance; on the other hand, when it is due to scurvy it must be considered specific in character and only to be remedied by specific therapy. In this respect it resembles the specific serum therapy of the infectious diseases. In this case (Chart 8) it will be noted that although orange juice also failed to bring about a gain, it immediately stimulated the appetite, which had reached a very low ebb; furthermore, it caused a marked improvement in the general condition and well-being of the infant. As the result of our own experience with wheat embryo and with middlings, we are of the opinion that both contain a certain amount of antiscorbutic substance, and that the embryo contains a decidedly greater amount. In neither of these parts of the wheat is specific vitamin present in a concentration comparable to that of orange juice. It may be contended that the amount of the embryo which we made use of was inadequate. In a sense this may

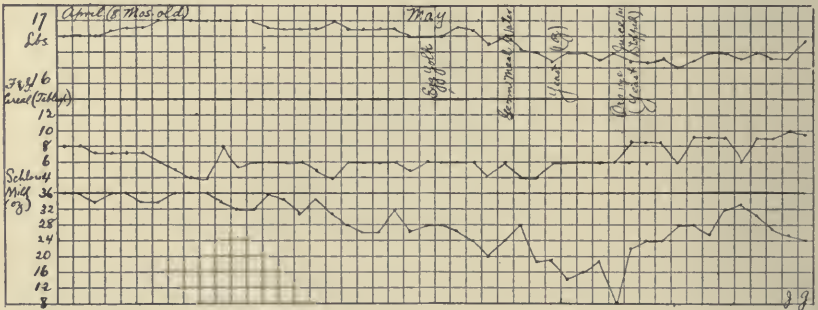

Chart 8.—Continuation of Chart 7; failure of egg yolk, germ meal extract and yeast as a curative antiscorbutic; improvement of appetite and general condition from orange juice.

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[7] McCollum, E. V., and Kennedy, C.: Jour. Biol. Chem., 1916, **24,** 491.

be true. However, from a dietetic point of view it is approximately as large a quantity as can be fed to infants.[8] Although the embryo cannot serve as antiscorbutic, there is a decided advantage in the use of germ meal cereal as well as of germ meal water, as they contain substance or substances which stimulate growth. There should be no misconception or confusion, however, as to their suitability, even in a prophylactic way, to replace orange juice. This is particularly to be regretted, as the preparation of a germ meal water which could be readily added to the milk instead of barley water would enable us to forego the necessity of giving our antiscorbutic food separately from the milk.

Charts 7, 8 and 9 show the daily weight for a period of six months of an infant who developed subacute scurvy, reproducing respectively the prescorbutic, the scorbutic and the reparative stages. In the second of these charts (Chart 8) it will be seen that although orange juice increased the appetite, it could not bring about a gain in weight even after it had been taken for two weeks. It shows, furthermore, that when orange juice was discontinued and replaced by a tablespoonful of mashed potato (boiled), a steady increase in weight set in, accompanied by a marked stimulation of the appetite, more especially for the fluid food. Accompanying this change there was a decided improvement in the general condition. A reaction of this kind raises the question, not merely as to whether one of these antiscorbutics is the more potent, but as to possible qualitative differences among them, and

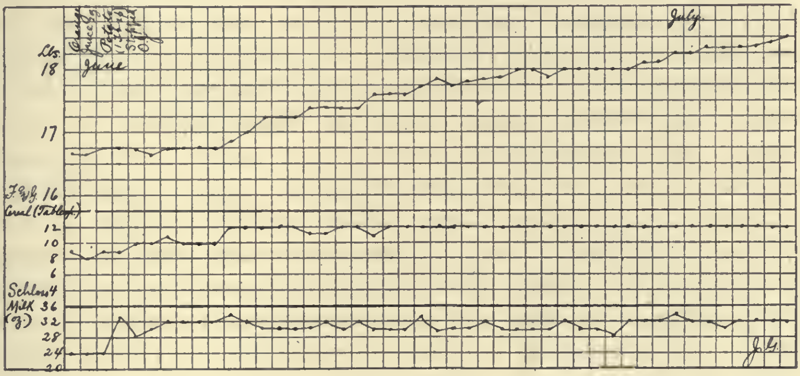

Chart 9.—Continuation of Chart 8; superior antiscorbutic effect of potato, in increasing appetite, in causing gain in weight and in improving the general condition.

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[8] Each tablespoonful of the cereal contained 1 gm. of dried embryo, so that the average infant took about 8 gm. a day in this form. Each quart of Schloss milk contained about 21 gm. of the watery extract. It will thus be seen that the infant depicted in Chart 8 received from 10 to 15 gm. of this active substance in addition to the cereal.

whether one may not be better suited to the needs of one child than to those of another. This is a question to which, as may be imagined, it is at present impossible to give a direct answer.

It is evident, however, that in this particular case one tablespoonful of potato was clearly more potent than one or even two tablespoonfuls of orange juice. In the paper by Hess and Fish[9] two mild cases of scurvy were mentioned, which developed in spite of a diet including vegetables. Reports of other observers would also lead to the conclusion that some infants are unable thoroughly to utilize certain well-established antiscorbutics. There are, for example, undoubted cases scattered through the literature which developed despite the use of orange juice, just as there are others which have manifested themselves notwithstanding a diet of raw cow's milk, or even, most rare of all, of breast milk. Finkelstein's[10] well-known experience of infantile scurvy developing in two successive children of a family, although prophylactic measures were employed to avoid the occurrence in the second infant, is a striking example of the fact that a definite metabolic disturbance of this kind may exist in certain persons and families, which cannot be counterbalanced by specific therapy. It is conceivable that orange juice, potato, green vegetables and other antiscorbutic articles of diet do not supply entirely the same essential substances; that these substances differ slightly in their chemical constitution, or that one food may contain more than a single substance of this nature. The fact that in some cases of subacute scurvy, although we meet with a prompt reaction to orange juice, we find that this good effect is enhanced by substituting potato, a result which has been witnessed several times, or that the beneficial effect of orange juice is still further intensified when a vegetable is added to the dietary, may be accounted for in this way.

A question perhaps of more theoretical than practical interest is that of the power of the body to store the vitamins. It is generally believed, and seems the most plausible explanation, that infants do not develop scurvy during the first few months of life on account of the fund of antiscorbutic material which they have inherited from their mothers and brought with them into the world. If in postnatal life these substances are not supplied, a negative balance ensues and infantile scurvy gradually results. An observation which we were in a position to make leads us to believe that the tissues have a remarkable power for storing antiscorbutic vitamins. The case is the one previously reported: an infant who had been markedly underfed before entering the institution and who gained for some months after admission, but then showed signs of subacute scurvy, such as periosteal tenderness, pallor, peridental hemorrhage, and tachycardia. One ounce of orange juice was given for a period of sixteen days, in other words, a pint in all. By this time the scorbutic symptoms were relieved, the hemorrhages into the gums were no longer to be seen, and the general condition was greatly improved; accordingly, the antiscorbutic diet was discontinued. This was the first of May. The infant weighed almost 14 pounds at this time, and was nearly 11 months old. During May he gained three quarters of a pound. Farina was then added to his diet, besides the 42 ounces of Schloss milk. In June he gained about 1½ pounds. He gained nothing in July, but showed no signs of scurvy. In August 1 ounce of orange was again given daily. Although no greater amount of food was consumed, there was at once an increase in weight, a gain of 12 ounces during the first week and an improvement in the general condition. We interpret these phenomena as indicating that the sixteen months of orange juice had protected the child for a period of two months and that he then lapsed into a condition of latent scurvy. A negative balance of vitamins was evident from the child's nutritional stagnation, considered in conjunction with the prompt growth reaction on the administration of orange juice.

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[9] Hess, A. F., and Fish, M.: Am. Jour. Dis. Child., 1914, **8**, 385.

[10] Finkelstein, H.: Lehrbuch der Säuglingskrankheit, 1912, **2**, 480.

CONCLUSIONS

As it had been shown that a clinical similarity exists between beriberi and infantile scurvy, it seemed as if yeast, which is a specific in the former disease, might also prove to be a potent antiscorbutic. Clinical experience did not substantiate the analogy, but demonstrated that this substance is of no value in scurvy either as a prophylactic or as a curative dietetic agent. It was found, however, to possess virtue as a stimulant to growth, when added to the milk in the form of the fluid autolyzed yeast or given to older infants as a desiccated powder.

The embryo or germ of the wheat seed is another effective therapeutic agent in the cure of beriberi or in avian polyneuritis. Accordingly, this was also tested clinically for its antiscorbutic power; for this purpose a cereal and a watery extract of the germ meal were prepared. These preparations manifested some value as antiscorbutics, but not sufficient to render them useful in this connection from a practical or clinical standpoint. The watery extract, which is readily prepared, was found to stimulate growth, and may be used to advantage, on account of this quality, as a substitute for barley in milk preparations.

It was furthermore noted that there is an idiosyncracy as to the reaction to well-established antiscorbutics; for example, in some instances orange juice may meet with only partial success while potato produces a rapid cure.

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EXPERIMENTAL STUDIES OF THE INTESTINAL FLORA *

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INTRODUCTION

The following experiments were carried out with the purpose of ascertaining the effect of various foods commonly used in infant feeding on the bacterial flora of the intestinal tract.

It was necessary to ascertain whether the number and variety of organisms varied in different parts of the intestinal tract. It is well recognized that but a small percentage of the bacteria occurring in the feces are viable. Bacteriologic studies of the feces, therefore, have justly been criticized on the ground that the findings give inaccurate data concerning the flora at other levels. Many workers in the field of the intestinal bacterial flora of infants have claimed that definite characteristic flora occur at certain parts of the intestinal tract. Attention has been called especially to the peculiarities of the duodenal flora.

Attention has been directed by many writers to the effect certain foods containing relative high percentages of carbohydrates or proteins have on the intestinal flora. Certain popular conceptions of the different types of intestinal disturbances in infants are based on the bacterial changes these foods are supposed to produce. If a diarrhea, for instance, occurs after a diet with a high carbohydrate content, this is called a "fermentative" condition. Under these circumstances the intestinal flora is considered to consist of organisms that act primarily on the carbohydrates. The products of this action are thought to produce the diarrhea. Similarly a disturbance associated with the feeding of a diet containing a high percentage of protein is considered to be due to "putrefaction."

It is a matter of dispute whether these intestinal disturbances are caused by primary chemical changes, or whether they are due to initial bacterial activity. As food containing a large amount of sugar is frequently associated with diarrhea in infants, studies were made to see

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* From the Department of Pediatrics and Bacteriology, Johns Hopkins University.

if the condition was accompanied by changes in the bacterial flora. Attention was paid not only to whether a change took place, but also at what level the change occurred.

Studies were made to determine the effect of starvation on the bacterial flora at different levels, both after a normal diet and after a diet which caused diarrhea.

EXPERIMENTAL STUDIES. SERIES 1

Technic.—The experiments were carried out on puppies a few weeks of age. The animals were cared for in a private house where ample space could be given for normal activities, as it was found that the animals after being weaned did very poorly under ordinary laboratory conditions. The attempt was made to eliminate from the series all animals with intestinal parasites. The technic employed for the study of the intestinal flora was as follows: The puppies were etherized, without previous administration of a sedative. A laparotomy was then performed under antiseptic precautions. After placing presection sutures and clamping the intestinal wall at a distance of about 3 to 5 cm. on either side of the suture, the gut was punctured with a medium sized record syringe needle and 3 c.c. of sterile saline introduced. This was drawn back into the syringe and the procedure repeated three or four times in order to insure a thoroughly mixed specimen of the fecal contents. Material was removed from the duodenum at the level of the tail of the pancreas, from the ileum about 8 cm. proximal to the ileocecal valve, and from the cecum about 8 cm. distal to the ileocecal valve. A specimen of the contents of the colon was also recovered in each experiment by means of a rectal tube. The animals made excellent operative recoveries.

The bacteriologic studies were carried out as follows: Two or more smears, stained by Gram's method, were made from the specimens recovered. Examination of these preparations gave helpful information as regards the actual presence of organisms, a general impression of the relative number present and a picture of the various types from a morphologic point of view. Four plates were made from each specimen on the following mediums: plain agar, dextrose litmus agar, 2 per cent. acid dextrose agar, and whey agar. Dilutions were not usually made from the duodenal and ileal specimens. In a few instances in which smears showed no organisms, or very few, cultures were made, after incubation of the specimen. Special studies for acidophilic organisms were carried out by making three transfers to 3 per cent. acid broth, after intervals of two days, and finally plating on 2 per cent. acid whey agar. As spore-bearing forms are easily inhibited by *Bacillus coli,* one specimen of the intestinal content, in each instance, was heated for fifteen minutes at 80 C., and then plated on the usual mediums.

GROUP 1. *Controls.*—Observations were first made on the intestinal contents of five puppies, which were used as controls. The diet consisted exclusively of whole milk (pasteurized), fed over a period of seven to ten days. The following experiments show the characteristic results.

These experiments show that the bacterial flora of young puppies fed on cow's milk is essentially the same as that of infants on a similar diet. The acidophilic bacilli found in small numbers in stools of infants fed on cow's milk were not noted in these studies. All the various organisms observed in the colon (the findings of the colon were identical with those of the cecum and have not been recorded) were found at the other levels. Fewer organisms, especially after ingestion of small amounts of food followed by periods of starvation, were found in the duodenum than elsewhere. There seems to be a gradual increase in the number of organisms from the duodenum to the cecum. Although *Bacillus coli* is the predominating type, the variety of organisms present is so great and their relative number so variable that one cannot speak of a characteristic flora at any level.

TABLE 1.—EXPERIMENT 6. NORMAL

Age	Diet	Fasting	Duodenum	Ileum	Cecum
1 mo.	Whole milk; 2 ounces at last feeding	4 hrs.	Smear: Organisms, +++[*] G— bacilli, ++ G+ cocci, + Large G+ bacilli and yeasts	Smear: Organisms, +++ G— bacilli, ++ G+ bacilli, + G+ cocci, — Spirillae, +	Smear: Organisms, +++ G— bacilli, ++ G+ bacilli, ++ G+ cocci, rare Spirillae, +
			Culture: B. coli and B. lactis-aerogenes, ++ Strep. lact., + Spore bearing forms, rare Acidophilic bacilli, 0	Culture: B. coli, ++ Acidophilic bacilli, 0	Culture: B. coli, ++ B. lactis-aerogenes, + Spore bearing forms, + Acidophilic bacilli, 0

[*] In this and the following tables +++ = very numerous, ++ = many, + = few, G = gram.

TABLE 2.—EXPERIMENT 9. NORMAL

Age	Diet	Fasting	Duodenum	Ileum	Cecum
1½ mos.	Whole milk; 1 ounce at last feeding	5 hrs.	Smear: Organisms, +++ G— bacilli, ++ G+ bacilli, ++ G+ cocci, rare	Smear: Organisms, +++ G+ bacilli, ++ G+ cocci, +	Smear: Organisms, +++ G— bacilli, ++ G+ bacilli, + Spirillae, + G+ cocci, +
			Culture: B. coli, + Strep. lact., rare Acidophilic bacilli, 0	Culture: B. coli, ++ Spore bearing forms Acidophilic bacilli, 0	Culture: B. coli, ++ Spore bearing forms, + Acidophilic bacilli, 0

TABLE 3.—EXPERIMENT 15. NORMAL

Age	Diet	Fasting	Duodenum	Ileum	Cecum
2½ mos.	Cow's milk for past 11 days; 2 ounces at last feeding	8 hrs.	Smear: Organisms, + G— bacilli, rare	Smear: Organisms, ++ G— bacilli, + G+ bacilli, rare G+ cocci, rare	Smear: Organisms, +++ G+ bacilli, rare G— bacilli, rare G+ cocci in clusters, +
			Culture: B. coli, rare Strep. lact. No acidophilic bacilli	Culture: B. coli, ++ Yeasts, rare Strep. lact., rare No acidophilic bacilli	Culture: B. coli, ++ Strep. lact., rare Yeasts, rare Spore bearing forms No acidophilic bacilli

GROUP 2. *Experiments with High Sugar Diets.*—Eleven puppies were fed pasteurized cow's milk, with additional lactose, four with additional sucrose. With rare exceptions the animals took this modification well. Typical experiments of this group are given.

TABLE 4.—EXPERIMENT 11. LACTOSE FEEDING

Age	Diet	Fasting	Duodenum	Ileum	Cecum
2 mos.	Milk +, 10% extra lactose for 9 days; amount last feeding, 2 ounces	2 hrs.	Smear: Organisms, + G— bacilli, + G+ cocci, rare G+ bacilli, rare	Smear: Organisms, +++ G+ bacilli, + G— bacilli, + G+ cocci, +	Smear: Organisms, +++ (poor definition) G— bacilli with + granular appearance G+ bacilli, + G+ cocci, rare
			Culture: B. coli, + B. lact.-aerog., + Spore bearing forms, + Strep. lact., + Acidophilic bacilli, 0	Culture: B. coli, ++ Strep. lact., rare Spore bearing forms, rare Acidophilic bacilli, 0	Culture: B. coli, ++ Strep. lact., + Spore bearing forms, + No acidophilic bacilli

TABLE 5.—EXPERIMENT 22. LACTOSE. FASTING AFTER DIARRHEA. STARVATION PERIOD 18 HOURS

Age	Diet	Period	Duodenum	Ileum	Cecum
1 mo.	Whole milk, 10% extra lactose; diarrhea, ++	4 days; 18 hrs. fasting	Smear: G+ bacilli, rare Organisms, rare (most fields no organisms)	Smear: G— bacilli, rare G+ bacilli, rare Most fields without organisms (rarely 1 to 5)	Smear: Organisms, +++ G— bacilli, + G+ bacilli, + G+ cocci, +
			Culture: Strep. lact., rare Spore bearing forms All isolated colonies 1-10 on a plate Acidophilic B., 0	Culture: Spore bearing forms B. coli, + B. lact. aerogenes (isolated colonies of above, 10-20 on a plate) Acidophilic B., 0	Culture: B. coli, ++ Spore bearing forms, ++ Strep. lact., ++ Acidophilic B., 0

TABLE 6.—EXPERIMENT 19. LACTOSE FEEDING (STARVATION)

Age	Diet	Starvation	Duodenum	Ileum	Cecum
2 mos.	Whole milk + 10% lactose; fed for past 10 days without diarrhea; amount last feeding, 2 ounces	20 hrs.	Smear: Organisms, rare* G— bacilli, rare	Smear: Organisms, rare, few† G— bacilli B+ bacilli G+ diplococcus	Smear: Organisms, +++ G— bacilli, ++ G+ bacilli (few) Spirillae G+ cocci
			Cultures: Strep. lact. B. coli Spore bearing forms (isolated colonies of each) Acidophilic bacilli, 0	Cultures: B. coli Strep. lact. Yeasts (few colonies of each) Acidophilic bacilli, 0	Cultures: B. coli and L. aerogenes, + Strep. lact. (many colonies of each) Acidophilic B., 0

* Rare; many fields without any organisms.
† Few, 2 to 5 in a field.

TABLE 7.—EXPERIMENT 25. LACTOSE WITH DIARRHEA (STARVATION)

Age	Diet	Fasting	Duodenum	Ileum	Cecum
7 wks.	Whole milk + 10% extra lactose for past 10 days; diarrhea 36 hrs. before operation (not at time of operation); 6 ounces at last feeding	20 hrs.	Smear: Organisms, + G— bacilli G+ cocci Culture: B. coli, + Strep. lact., + (scattered colonies of each) No acidophilic bacilli Presence of spore bearing forms Mesentericus; large spreading colonies	Smear: Organisms, ++ G— bacilli, + G+ bacilli, + Culture: B. coli, + Strep. lact., + Spore bearers, + No acidophilic bacilli Presence of spore bearing forms Profuse growth; mesentericus and cereus	Smear: Organisms, +++ G— bacilli, + G+ bacilli, + G+ cocci, + Culture: Strep. lact., + B. coli, ++ No acidophilic bacilli Presence of spore bearing forms Colonies of mesentericus subtilis (pseudotetanus)

TABLE 8.—EXPERIMENT 14. CANE SUGAR

Age	Diet	Starvation Period	Duodenum	Ileum	Cecum
2½ mos.	Whole milk with cane sugar to 13%	7 hrs.	Smear: Organisms, + G. bacilli G+ bacilli G+ cocci, all rare Culture: B. coli Acidophilic organisms, 0 Spore bearing forms, +	Smear: Organisms, + G— bacilli, + G+ bacilli, + Culture: B. coli, rare Acidophilic, 0 (desquamated epithelial cells)	Smear: Organisms, +++ G— bacilli, ++ G+ cocci, rare Culture: B. coli, ++ Strep. lact. Strep. (fecalis) Acidophilic bacilli, 0

The studies of the bacterial flora of puppies fed diets containing from 10 to 15 per cent. of lactose or sucrose show that the same organisms are present as under normal dietary conditions. Even with diets with a very high carbohydrate content, no acidophilic organisms are present at any level. As in the previous group of experiments, there is a close agreement between the microscopic and cultural findings. Examination of the intestinal contents of puppies with a profuse diarrhea after a high carbohydrate diet show no essential variation from the findings previously noted. The same diminution in the number of organisms after starvation is noted in this group of experiments as in the foregoing.

In addition to the effect of dietary changes on the intestinal bacterial flora, the results of the foregoing experiments show that after periods of starvation of from eight to twenty hours, the number of organisms in the small intestine is greatly reduced. This diminution is more marked in the duodenum, but is evident as far down as the cecum. The reduction in the number of organisms seems to be in proportion to the length of the fasting period and the amount of food taken before the starvation, the longer periods of fasting and the previous ingestion of little food giving the greatest reduction in organisms. Although many of the plates and smears from specimens under those conditions showed no organisms, in every experiment bacteria were demonstrated at each level. No changes in types of organisms were shown to exist after periods of fasting.

GROUP 3. *Protein Milk Diet.*—Some difficulty was experienced in feeding the puppies protein milk. In but one instance did the animal take this well.

TABLE 9.—EXPERIMENT 10 (PROTEIN MILK)

Age	Diet	Fasting	Duodenum	Ileum	Cecum
2 mos.	Protein milk; 2 ounces last feeding partially vomited	2 hrs.	Smear: Organisms, ++ G— bacilli, + G+ bacilli G+ cocci Culture: B. coli and B. lact. aerogenes, ++ Special test for spore bearing forms, + Acidophilic, 0	Smear: Organisms, +++ G— bacilli, ++ G+ cocci, + G+ bacilli Culture: B. coli, ++ Spore bearing forms, +	Smear: Organisms, +++ G— bacilli and spirillae, ++ G+ bacilli and cocci, ++ Culture: B. coli, ++ Spore bearing forms, +

TABLE 10.—EXPERIMENT 24. PRESENCE OF SPORE BEARING FORMS

Age	Diet	Fasting	Duodenum	Ileum	Cecum
2 mos.	15% lactose without diarrhea; period feeding, 1 week; 4 ounces last feeding	20 hrs.	No growth	Many colonies of spore bearing forms mesentericus cereus subtilis yeasts	Few colonies of spore bearing forms mesentericus

The bacterial intestinal flora of a dog fed on protein milk is essentially the same as was found under normal dietary conditions. Although the spore-bearing forms are more numerous, they do not become the predominating type. It is seen that spore-bearing organisms occur at all levels in relatively large numbers, in animals fed on a diet high either in carbohydrates or in proteins.

EXPERIMENTAL STUDIES. SERIES 2

A second series of studies was made on infants. A duodenal catheter was passed, as has been described by Hess,[1] and duodenal con-

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1. Hess, A. F.: The Use of a Simple Duodenal Catheter in the Diagnosis and Treatment of Certain Cases of Vomiting in Infants, AM. JOUR. DIS. CHILD., 1912, **3**, 133.

tents were then aspirated. The specimens were studied as in the foregoing series of experiments. Typical reports of this series are given below. Ten cases were studied.

TABLE 11.—STUDY 2

Subject	Diet	Hours after Feeding	Results
Baby B., aged 5 mos.; normal	Whole milk	2	1. 5 c.c. of yellow turbid material with soft whitish curds; recovered 2. Smear: Organisms, +++ (not unlike fecal specimen); gram ++ cocci; gram — bacilli 3. Cultures: Staphylococci, +; Streptococcus lacticus, +; B. coli and Lactis aerogenes, ++; yeasts and spore bearing forms, rare

TABLE 12.—STUDY 4

Subject	Diet	Hours after Feeding	Results
Normal, 4 months' infant	Whole milk modification	2	1. ¾ c.c. rather viscid, yellow, turbid material 2. Smear: Organisms, ++; gram— bacilli, +; gram+ cocci, + 3. Culture: B. coli and B. lactis-aerogenes, +

TABLE 13.—STUDY 5, BY MODIFICATION OF FORMER TECHNIC *

Subject	Diet	Hours after Feeding	Results
Normal, 5 months' infant	Breast milk, with supplementary feedings of cow's milk	5	1. Small amount (0.5 c.c.) slightly turbid fluid 2. Smear: No organisms noted 3. Cultures: B. coli, rare; B. lactis-aerogenes, +; Streptococcus lacticus, +

* In this instance, 10 c.c. of normal saline was introduced into the duodenum before aspiration.

The observations made on infants by means of a duodenal catheter show that not only a large number of organisms may be present in the duodenum, but that these may be very similar to the organisms occurring in the feces. Cocci of various types are more numerous in the duodenum than are commonly found in the fecal specimens. The predominating organisms at this level when large numbers of forms are present is a gram-negative bacillus; these are *Bacillus coli* and *Bacillus lactis-aerogenes.* It will be noted that the coccus forms referred to above are similar to those present normally in the mouth.

DISCUSSION

Localization of Flora.—From the experiments recorded it is seen that the flora of the intestinal tract at various levels is essentially the same, as determined by our present bacteriologic methods. Although the organisms recovered from the feces showed poorer definition and staining properties than those recovered from other levels, the same types of organisms were noted microscopically, and culturally they were found to be nearly the same in all regions. It seems, therefore, that the study of fecal specimens gives quite a true, adequate picture of the flora that may occur at any of the different levels of the entire intestinal tract. It is of special interest to find that so many forms may be present in the duodenum of the normal infant, and that these may be very similar to forms found at lower levels. It has not infrequently been stated that such a condition was in all probability associated with gastro-intestinal disorders. Tobler[2] asserts that the digestive processes of the duodenum are unaccompanied by the activities of bacteria. The method of recovering the specimens with the duodenal catheter is not entirely satisfactory, as it is impossible to avoid completely contaminations from the mouth and upper alimentary tract. In regard to the relative number of organisms present at the various levels, the experiments show that during the early periods of digestion there is no recognizable variation. Where so many organisms are present, we feel that we have no satisfactory method of determining with sufficient accuracy an estimate of the absolute number.

Effect of Diet on the Flora.—Moro[3] and others have called attention to changes in the bacterial flora of infant stools after various diets. An acidophilic, gram-positive group of bacilli was considered characteristic of infants fed on breast milk. The feces of children fed on cow's milk was found to contain few of these organisms and numerous *B. coli, cocci* and proteolytic forms. Wollstein[4] investigated stools of infants fed on high protein and carbohydrate diets. On carbohydrate high diet, "cocci, colon bacilli, acidophilus and bifidus bacilli were most numerous." "During the periods of high protein content in the food, *B. mesentericus* gained the ascendancy, *B. aerogenes-capsulatus* sometimes persisted, and the colon bacilli were increased in numbers. But the acidophilus and bifidus did not entirely disappear." From the writings of these authors it is to be assumed that in their belief certain quantitative changes result from varying the food. Herter and

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[2] Tobler, L., and Bessau, G.: Krankheiten durch abnormen Ablauf der Ernährungsvorgänge und des Stoffwechsels, 1914.

[3] Moro, E.: Jahrb. f. Kinderh., 1900, **52,** 38.

[4] Holt, L. E.; Brown, A.; Wollstein, M., and Courtney, A. M.: The Influence of High Protein Feeding on the General Metabolism, on the Intestinal Flora and on the Body Temperature of Infants, Am. Jour. Dis. Child., 1912, **4,** 265.

Kendall[5] fed monkeys and cats high protein diet and assert that a proteolytic flora was obtained.

Few experimental studies of the intestinal bacteriology of animals, after changes in diets, have been made. Rettger and Horton[6] showed that when rats were fed on a diet containing a single protein the intestinal flora became simpler. The normal flora was replaced by the acidophilic group of organisms. The authors consider that the change was "independent of the pure proteins, but bore a definite relation to the protein-free milk which formed a part of the pure protein diet." From a more recent series of experiments, Rettger[7] concludes that the intestinal flora of white rats and the domestic fowl undergoes "profound alterations" when fed on a milk diet. These changes consist in the establishment of a flora consisting of *Bacillus acidophilus* or *Bacillus bifidus,* or both of these organisms may predominate. From a further series of experiments carried out on rats fed various carbohydrates, Rettger[8] concludes that lactose in itself will cause the changes above mentioned.

Of special interest were the findings in the experiments as presented by me after feeding cow's milk containing relative high percentages of additional sugars. The flora was not only unchanged in the colon, but all the levels examined showed essentially the same organisms as after diets of unmodified cow's milk. An acidophilic flora, as noted by Rettger, in the sense of a predominating gram-positive bacillus, showing cultural characteristics of *Bacillus bifidus* and *Bacillus acidophilus,* or both of these organisms, was never obtained, either after lactose or sucrose feedings. It is possible that the difference in the species of the animals utilized for experimentation may in part explain these contradictory results. The cultural methods employed to isolate the acidophilic organisms may, indeed, have failed to show the presence of rare bacilli of this type. That they never were in predominating numbers is shown conclusively by the microscopic findings, as a smear made up chiefly of gram-positive bacilli was never encountered.

It is very difficult to say whether the diarrhea elicited by the high sugar feedings in these experiments is similar to that occurring in infants under similar conditions. The animals, in many instances, became inactive, would not play and took their feedings poorly. The diarrhea was easily controlled by withdrawing the sugar from the diet. The younger puppies developed diarrhea much more quickly than older ones.

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[5] Herter, C. A., and Kendall, A. I.: Jour. Biol. Chem., 1908-1909, **5,** 293.

[6] Rettger, L. F., and Horton, G. D.: Centralbl. f. Bakteriol., Part 1, Orig., 1914, **73,** 362.

[7] Rettger, L. F.: Jour. Exper. Med., 1915, **21,** 365.

[8] Rettger, L. F.: Footnotes 6 and 7.

The experiments with protein milk are too few to allow definite conclusions. Nevertheless, it seems significant that essentially the same types of organisms may be present in the intestinal tract on this diet as on unmodified cow's milk. It is possible that the organisms normally present under dietary conditions may change their function and act on proteins instead of carbohydrates. The reason for the beneficial effect of protein milk must still be considered as a matter of conjecture.

From those studies it seems probable that protein milk induces no marked alteration in the bacterial flora, and that, therefore, the changes produced in digestion are primarily chemical rather than bacteriologic. The fact that spore-bearing forms were found at all levels examined deserves mention. It has formerly been thought that these organisms sporulated primarily in the colon and there produced toxic compounds which caused certain digestive disturbances. In puppies, it is clear that the spore-bearing forms may occur in large numbers at upper levels of the intestinal tract without causing any unfavorable symptoms. The same statement is undoubtedly true for infants, as foods such as protein milk are known to contain large numbers of these forms, and it has been shown by Ford and Knox[9] that the ingestion of these organisms may cause no clinical symptoms.

In relation to the experiments on the effects of starvation presented in this paper, reference should also be made to the work of Cushing and Livingood.[10] These authors made observations on the number of intestinal organisms in dogs after a twenty-four-hour fast. A laparotomy was performed on an adult dog previously fed on a milk diet and starved for twenty-four hours. Specimens were then taken from ten different levels, after incision of the intestine. The specimens consisted of single platinum loopfuls of intestinal contents. Smears and cultures were made. No mention is made either of the mediums used or the method employed for counting the organisms. It should be stated that a single loopful of intestinal contents may vary so much in consistency and in number of bacteria present that estimations of the number and kind of organisms by this method are of very relative value. From their experiments the authors conclude that a relative amicrobism of the small intestine results after a period of twenty-four hours' starvation. Study of the distal loops of two patients with permanent fistula of the jejunum showed a sterile condition. These and further

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9. Knox, J. H. M., Jr., and Ford, W. W.: Bull. Johns Hopkins Hosp., 1915, **26,** 27.

10. Cushing and Livingood, L. E.: Contributions to the Science of Medicine, by Pupils of Welch, 1900, p. 543.

observations on a series of twenty-seven dogs and eight rabbits confirmed the conclusion given above. These last experiments were undertaken from a surgical rather than from a strict bacteriologic point of view. Careful dietary precautions were not taken. These authors also conclude from their experimental studies that one is not justified in speaking of a local flora at particular levels.

Effects of Starvation.—The examinations of the intestinal contents after periods of starvation show definite changes in the number of organisms. In many instances smears showed rare forms, and many times the plates showed but isolated colonies, in contrast to the profuse growth found normally. Changes in the kinds of organisms persisting after periods of starvation were not noted. The greatest diminution was observed in the duodenum. In some instances, however, only rare organisms were present in the contents of the ileum. The contrast between the paucity of organisms at this level and the large number present in the cecum was striking. Although the number of organisms is, to a great extent, dependent on the food residue present, absolutely sterile specimens, even after the food residue was undoubtedly absent, were never obtained. In other words, the condition produced by starvation is one of relative amicrobism.

CONCLUSIONS

From the experimental studies on the intestinal flora of puppies, the following conclusions can be drawn:

1. In puppies the types of organisms occurring at the duodenum, ileum, cecum and rectum are in all instances similar. One cannot speak of a characteristic local flora occurring in these regions.

2. Feedings to puppies of cow's milk mixtures with high percentage of sucrose or lactose does not cause characteristic changes in the intestinal flora at any level, even when a diarrhea is produced.

3. Starvation of twenty-four hours renders a relative amicrobism of the small intestine.

THE HEMATOLOGY OF INFECTIOUS DIARRHEA *

CHARLES J. BLOOM, B.Sc., M.D.
NEW ORLEANS

In reviewing literature relative to this subject, the writer has found a total absence of any authentic conclusions regarding the blood in infectious diarrhea. Starr,[1] Whipham[2] and Keating[3] make no mention of the blood whatsoever. Taylor and Wells,[4] Ashby and Wright,[5] Carmichael[6] and Oppenheim[7] also failed to mention this important point. The textbooks of Donkin,[8] Smith,[9] Carr[10] and Cotton[11] have left unsaid all matters pertaining to this subject. Even the most recent works on pediatrics, by such authorities as Koplik,[12] Hutchinson,[13] Chapin and Pisek,[14] Rachford,[15] Cautley,[16] Fischer,[17] McCaw,[18] Rotch,[19] Still,[20] Holt,[21] Garrod, Batten, Thursfield[22] and Morse,[23] have all left this important topic untouched. In addition, a careful survey of the works of different authorities who have made hematology a special study in the majority failed to record even a single fact on this subject. Buchanan,[24] Ward,[25] Schleip,[26] Pappenheim[27] and Naegeli[28]

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* Submitted for publication July 10, 1916.
* From the Boston Floating Hospital, Clinical Pathologist, August, 1914.

[1] Starr: Diseases of Digestive Organs.
[2] Whipham: Medical Diseases of Children.
[3] Keating: Encyclopedia Diseases of Children.
[4] Taylor and Wells: Diseases of Children.
[5] Ashby and Wright: The Diseases of Children.
[6] Carmichael: Diseases of Children.
[7] Oppenheim: The Medical Diseases of Childhood.
[8] Donkin: Diseases of Childhood.
[9] Smith: Eustace, Diseases of Children.
[10] Carr: The Practice of Pediatrics.
[11] Cotton: Diseases of Infancy and Childhood.
[12] Koplik: Diseases of Infancy and Childhood.
[13] Hutchinson: Lectures on Diseases of Children.
[14] Chapin and Pisek: Diseases of Infants and Children.
[15] Rachford: Diseases of Children.
[16] Cautley: Diseases of Children.
[17] Fischer: Diseases of Infancy and Children.
[18] McCaw: Diseases of Children.
[19] Rotch: Pediatrics of Children.
[20] Still: Common Disorders and Diseases of Childhood.
[21] Holt: Diseases of Infancy and Childhood.
[22] Garrod, Batten and Thursfield: Diseases of Children.
[23] Morse: Case Histories in Pediatrics.
[24] Buchanan: The Blood in Health and Disease, Oxford Medical Series.
[25] Ward: Clinical Haematology.
[26] Schleip: Technik der Blutuntersuchung.
[27] Pappenheim: Atlas der menschlichen Blutzellen.
[28] Naegeli: Blutkrankheiten und Blutdiagnostic.

have ignored this question in its entirety. Gulland and Goodall[29] say: "In severe cases there may be high counts from concentrations of blood. The casual conditions may cause alteration in the number or proportion of the white cells. In chronic cases there may be severe anemia." Even in the volumes of Pfaundler and Schlossmann[30] there is the failure to record any of these facts.

METHOD OF WORK

The month of August proved ideal in every respect, for there were variations in temperature, and all types of infectious diarrhea were portrayed, and a sufficient number to justify conclusions under the different lines of research. For convenience and also for thoroughness it was thought preferable to divide the infectious diarrheas into three groups: Group 1 to contain the cases in which the etiologic factor was the *Bacillus dysenteriae* (number of cases, sixteen); Group 2, the causative factor being the *B. welchii* (*B. aerogenes-capsulatus*) (number of cases, five), and Group 3, containing the cases with a mixed infection (number of cases, four). In all, a total of twenty-five cases were studied and watched in a detailed manner. The organisms found under the third group included *B. welchii, B. paratyphosus, B. typhosus* and streptococci. Indeed, I am glad I made these studies, because there were several important facts made out which would otherwise have been omitted.

Each morning the bacteriologist gave me a list of new cases, namely, those which were suggestive from the clinical manifestations alone. I then, on the same day, began the investigation from the hematologic standpoint. Every other day a total leukocyte count and a differential were made on the cases while in the acute stage. During the convalescent period the blood was examined not less frequently than every fourth day. In this way I studied the case from the admission and followed each one until the bacteriologic evidences for our work became negative for three successive examinations. During the period of research there were over fifty cases followed, and I have chosen twenty-five of this number, because a great many of the remaining cases proved to be other than infectious diarrhea, although clinically a number of them were thought to come within this group. The number of blood pictures per case was not less than five and not more than ten. Every day a visit in person to the individual patients was made and notations were recorded. One day out of each week the work for the previous six days was recapitulated, and if it was felt that more time was needed, the writer took an additional half day. It is hoped that the facts obtained along this line will be the stimulus for additional work, for indeed the blood manifestations of dysentery have in the past received little attention.

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[29] Gulland and Goodall: The Blood.

[30] Pfaundler and Schlossman: Atlas, Diseases of Children.

CLASSIFICATION

After a careful survey of the cases in question I have endeavored to classify them from a bacteriologic point of view,[31] this referring only to those which have been seen in person:

Infectious diarrhea
  I. Toxic
    1. Flexner
      a. Severe
      b. Moderate
      c. Mild
  II. Nontoxic
    2. Welchii
      a. Severe
      b. Moderate
      c. Mild
    3. Mixed
      a. Severe
      b. Moderate
      c. Mild

In the severe form of the toxic type there are marked prostration, coma, great loss in weight, ruby lips, temperature of 103 persisting, dejections ten to twenty-five daily, on the one hand, or two to four, on the other, and inability to retain by mouth any food whatever.

In the moderate form of this type the symptoms given above are slightly less severe, with a temperature of not over 103, of a remitting character. Only a few dejections in this type are a rare occurrence.

In the mild form of the toxic type there is no coma, the prostration is slight, and the weight remains about uniform; there are no apparent neurologic symptoms, no perceptible loss of interest in the surroundings, and the temperature rarely reaches 101.

In the severe form of each of the two divisions of the nontoxic type the symptoms resemble those of the severe cases in the toxic group in every respect except that the coma is not as a rule so well marked and prostration does not seem to be at all proportional to the temperature and infection. The amount of fever is generally higher, particularly in the mixed infection in which the *B. welchii* is one of the organisms.

The moderate cases of these two divisions of the nontoxic group differ from the severe cases only in the lower temperature, with slight prostration, and the absence of nervous symptoms.

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[31] From a bacteriologic standpoint as exhibited, August, 1914.

The mild cases of the nontoxic group manifest some peculiarities. The child appears to be slightly ill, but is interested in the surroundings, and if old enough will talk, sit up in bed and do many things appertaining to its age. Diarrhea is a constant symptom, though the loss in weight is not so great as the number of dejections would lead one to expect. Bacterial manifestations are present and one finds them in almost every examination of the stool. The patients of this group have practically no abnormalities with respect to temperature, pulse or respiration; in other words, if it were not for the diarrhea you could hardly consider the children ill, yet this condition may be the forerunner of the other two types of the disease.

TABLE 1.—The Character of the Disease and the Result in Twenty-Five Cases of Infectious Diarrhea

Character	Severity	Case Number *	Recovered	Died
Toxic	Severe	1 D., 3 D., 4 D., 10 D., 16 D.	0	5
	Moderate	11 R., 14 R., 2 D., 5 R., 6 D., 7 R., 8 D.	4	3
	Mild	9 R., 12 R., 13 R., 15 R.	4 — 8	0 — 8
Nontoxic	Severe	20 D., 21 D.	0	2
	Moderate	22 R., 19 R.	2	0
	Mild	25 D., 17 R., 18 D., 23 R., 24 R.	3 — 5	2 — 4
			13	12

* In this column D. signifies that the patient died, R. that he recovered.

TEMPERATURE

The temperature curve in infectious diarrhea is indeed variable. The first week of illness the temperature ascends gradually, reaching as a rule the maximum from the fifth to the seventh day, although occasionally the maximum will not be reached before the beginning of the second week, with a morning remission and an evening rise during the entire fever period.

In the second week of illness the maximum temperature reached is usually from 1 to 1.5 degrees less than that of the first week.

In the third week of illness the temperature rarely exceeds 100, and most often reaches a maximum in the neighborhood of 99 and a fraction.

In the fourth week of illness the patient is generally free from fever; occasionally a slight rise to a point not exceeding 99.5 may be recorded for one day. This is due to some indiscretion and is not to be considered a part of the real curve.

The maximum temperature over 103 means the prophecy of death. Other cases in which we have an initial temperature over 105, and this followed by a fall of from 2 to 3 degrees, for the most part terminate fatally anyway. In trying to determine whether there was any direct relation between the temperature and the pulse, as contrasted in typhoid fever, the following are the results obtained:

TABLE 2.—Duration of Fever and Percentage of Deaths in Twenty-Five Cases of Infectious Diarrhea

Number Cases	Number Days with Fever	Per Cent. Cases	Per Cent. Died
1	20	4	0
1	19	4	0
1	17	4	0
1	15	4	0
4	14	16	8
2	13	8	0
1	12	4	4
2	11	8	8
1	10	4	0
1	9	4	4
1	8	4	0
4	6	16	16
1	5	4	0
1	4	4	4
1	3	4	0
1	2	4	4
1	1	4	4

TABLE 3.—Duration of Fever Summarized in Five-Day Periods *

Number Cases	Number Days with Fever	Per Cent. Cases	Per Cent. Died
1	20	4	0
3	15	12	0
10	10	40	5
7	5	28	4
4	1	16	3

* The patients averaged ten days of fever while in the hospital.

In Flexner bacillus diarrhea, as an illustration of the pulse and temperature relation, a child of 10 months showed a temperature of 104.5 and a pulse of 120. If the pulse is taken when the child is crying,

TABLE 4.—PERCENTAGE OF PERIOD SPENT IN HOSPITAL

Number Cases	Per Cent. Time in Hospital
9	100
2	90
2	80
1	70
5	60
2	50
2	40
0	30
1	20
1	10

TABLE 5.—SUMMARY OF PERCENTAGE OF PERIOD SPENT IN HOSPITAL

Number Cases	Per Cent. Time in Hospital	Number Died
14	70	9
7	50	3
2	30	0
2	10	0

TABLE 6.—RANGE OF TEMPERATURE

Number Cases	Temperature	Per Cent. Total Number	Per Cent. Died
1	106+	4	4
2	105+	8	8
4	104+	16	16
2	103+	8	4
6	102+	24	12
7	101+	28	0
3	100+	12	4

TABLE 7.—SUMMARY OF RANGE OF TEMPERATURE

Number Cases	Temperature	Per Cent. Total Number	Per Cent. Died
7	104+	28	28
8	102+	32	16
10	100+	40	4

TABLE 8.—Duration of Illness

Prior to Admission		After Admission	
Cases	Days	Cases	Days
Group 1		Group 1	
1	1	2	2
1	2½	2	2
4	3	1	7
1	4	1	11
1	6	4	13
3	7	3	14
1	8	1	16
1	13	1	20
3	14	1	21
		1	30
Group 2		Group 2	
2	3	1	6
1	7	1	10
2	14	1	11
		1	12
		1	21
Group 3		Group 3	
1	7	1	10
1	10	1	20
1	14	2	21
1	21		
Total		Total	
1	1	2	2
1	2½	2	2
6	3	1	6
1	4	1	7
1	6	2	10
5	7	2	11
1	8	1	12
1	10	4	13
1	13	3	14
6	14	1	16
1	21	2	20
		4	21
		1	30

and this is the case in the majority of instances, of course the rate will be much greater; but, on the other hand, if it is taken when the child is at rest, as a rule a high temperature and a low pulse will be obtained, very similar to the condition in typhoid.

In the second or Welch's bacillus group the results obtained vary markedly from those of the former. As an illustration, a child of 7 months showed a temperature of 100 and a pulse of 150. This typifies a peculiar combination, namely, a rather low temperature and a greatly accelerated pulse.

TABLE 9.—Total Duration of Illness Arranged by Groups

Case	Duration, Days	Case	Duration, Days
Group 1		Group 2	
1	11	1	13
2	14	1	18
2	16	1	20
1	17	1	26
1	18	1	45
2	20	Group 3	
1	21	1	17
2	23	1	30
1	26	1	35
1	29	1	42
1	44		

TABLE 10.—Total Duration of Illness *

Case	Duration, Days	Case	Duration, Days
1	11	2	26
1	13	1	29
2	14	1	30
2	16	1	35
2	17	1	42
2	18	1	44
3	20	1	45
1	21		
2	23	Average	23

* Case 5 has been omitted.

The cases under the group of mixed infection simulate those classified under the previous one, with the exception that the pulse is more greatly accelerated, particularly if the mixed infection contains both the *B. welchii* and streptococci.

Fever is one of the symptoms on which a degree of prognostication can be based. The limits were from 100 to 106 and a fraction. All patients who had a temperature above 104 died, and a few of those whose temperature reached but a fraction above 102 succumbed.

Of those who died, 77 per cent. succumbed in less than twenty days, and the remaining 23 per cent. died between the twenty-first and twenty-sixth days. Of those who recovered, 27 per cent. were sick under twenty days, 28 per cent. between twenty-one and thirty days, 18 per cent. between thirty and forty days and 28 per cent. between forty and fifty days.

TYPICAL CASES

Case 13 (Group 1).—W. D. was the youngest of three children, having two sisters, aged 3 and 4 years, respectively. His father was 26 and his mother 23 years old, and both give a history of good health. There had been no known exposure to tuberculosis or to infectious diseases and no history of syphilis. The child was born at full term in normal delivery and was not ill until February, when he had bronchitis for three weeks. He was breast fed for ten months and after that time received various modifications of condensed milk with crackers and bread added to the diet.

TABLE 11.—Blood Finding in the Case of W. D.

Date	Leukocytes	Large	Small	Neutrophils	Transitionals	Türck's Cells
8/ 2/14	8,600	7	19	68	1	5
8/ 4/14	12,100	9	36	49	5	1
8/ 8/14*	9,400	4	32	60	..	4
8/11/14	14,800	6	26	60	2	0
8/17/14	10,600					
8/20/14	12,800	8	60	32		
8/22/14	10,400	10	36	48		
8/25/14	12,400	2	56	36	6	
8/29/14	16,600	2	42	56		
8/30/14	15,800	4	44	52		

* Entered on the sixteenth day of illness, convalescent from Aug. 8, 1914, on.

He had been ill for two weeks at the time of admission, suffering with vomiting and diarrhea, the vomiting immediately following the intake of food. The diarrhea consisted of fifteen movements in twenty-four hours, green in color, watery in consistency, foul in odor, and containing blood and mucus. He had had fever one day, seemed somewhat prostrated and slept poorly.

Physical examination showed nutrition and development good. The cheeks were somewhat flushed and the general appearance indicated that the child was ill. The anterior fontanel was open, measuring 1.5 by 1.5 cm. There was a slight rosary, but enlargement of the epiphyses and rigidity and retraction of neck were negative. The pupils and the eyes in general, the tongue and the mouth seemed normal. He had four teeth above and two below. There were no enlarged glands and the drums of the ears were not pathologic. The heart was normal for a person of the patient's age. The left border of dulness was

4.5 cm. to the left of the midsternal line, and 0.5 cm. inside the nipple line; the right border was 2.5 cm. to the right of the midsternal line. The sounds were regular and no murmurs were heard. The lungs showed no pathologic conditions. The abdomen protruded slightly, and there were physical signs of tympanites. The liver dulness extended from the fifth rib to 2 cm. below the edge of the costal border. The genitalia were negative. The skin was soft, elastic, warm and of good color.

Laboratory findings on Aug. 13, 1914, showed *B. dysenteriae* — Flexner — positive; von Pirquet negative on Aug. 6, 1914.

The blood findings in the case of W. D. may be compared to those of another patient with the toxic type of moderate severity.

CASE 19 (Group 2).—R. G. was the youngest of four children. Her father died at the age of 29 from a paralytic stroke. The brothers and the sister were in good health. The mother gave a history of one miscarriage. There had been no known exposure to tuberculosis or infectious diseases. The child's birth weight was 10 pounds. She had an easy birth, being born at full term without the use of instruments. She was nursed for one month, and then Mellen's food in variable proportions was substituted until the child was 6 months of age. After that time she took bread and crackers and modifications of whole milk.

TABLE 12.—BLOOD FINDINGS IN A CASE OF TOXIC TYPE OF MODERATE SEVERITY

Date	Leukocytes	Large	Small	Neutrophils	Transitionals	Türck's Cells
8/ 8/14*	5,800	12	44	40	4	0
8/11/14	8,600	8	20	72	0	0
8/14/14	9,000	6	42	52	0	0
8/17/14	7,600	..	..	..	0	0
8/20/14	6,600	2	64	34	0	0
8/22/14	8,800	2	30	68	0	0
8/25/14	6,800	2	40	58	0	0
8/28/14	6,400	0	50	46	2	2
8/29/14	5,800	2	50	46	2	0

* Entered on the ninth day of illness.

Three weeks before the child was examined, when she was recovering from pertussis, she developed diarrhea. With the diarrhea there were fever and vomiting. Vomiting persisted after the initial attack, being irregular in frequency and occurring immediately after feedings. The amount vomited equaled the amount of food taken, the vomitus being curdled. The diarrhea was very severe, the movements numbering from ten to fourteen a day, green in color, watery in consistency, foul in odor and containing a few curds, much blood and a large quantity of mucus, but the prostration was moderate in degree.

Physical examination showed the child to be of poor development and nutrition. Her general appearance, however, was fair. Her head was round, the posterior fontanel was closed and there was no craniotabes present. The anterior fontanel measured 3.5 by 3 cm. The pupils were clear and responded to light and accommodation. The tongue and mouth seemed normal. The throat was clean and there was no evidence of dentition. There was no discharge from the ears; the glands were negative. Heart, lungs, abdomen and genitalia gave no evidence of a pathologic condition. The liver was slightly enlarged and was 2 cm. below the costal border. The reflexes were present, but not exaggerated. There was no paralysis or muscular spasm, and Kernig and Babinski signs were absent. The skin was dry, soft and elastic. She had a slight erythema on her back and her buttocks were excoriated.

On Aug. 12, 1914, laboratory examination showed *B. welchii* triple plus.

Case 23 (Group 3).—E. B. was the youngest child of healthy parents of French extraction. The other children were in good health. The family history was entirely negative. The child was born at full term and was normal at birth. The mother thought the child weighed 7 pounds at birth. The baby, unfortunately, received no breast milk. A modification of whole milk of the formula 2-6-1.6 was given her for two weeks. This, however, did not agree with her. Malted milk was next tried in varying proportions, and the child seemed to thrive much better.

TABLE 13.—Laboratory Findings in the Case of R. G.

Date	Leukocytes	Large	Small	Transitionals	Neutrophils	Myelocytes
8/12/14	9,400	2	50	2	46	
8/13/14	17,600	12	54	..	34	
8/15/14	10,800	2	26	4	62	6
8/19/14	18,000	2	82	..	16	
8/21/14	13,600	4	60	..	34	
8/24/14	20,500	4	86	..	10	
8/26/14	16,400	4	50	..	56	
8/29/14	9,400	..	40	..	60	

TABLE 14.—Laboratory Findings in the Case of E. B.

Date	Leukocytes	Large	Small	Neutrophils	Transitionals	Eosinophils	Türck's Cells
8/13/14	10,200	0	40	60			
8/15/14	30,400	12	36	52	4		
8/19/14	16,800	4	28	76	2		
8/21/14	15,000	2	34	64			
8/24/14	12,400	2	60	36	..	2	
8/26/14	14,200	4	56	36	4		
8/29/14	14,000	2	52	44	..	..	2

Two days prior to admission the child started to vomit forcibly, and each spell of vomiting was accompanied by a dejection. This occurred with each feeding. At the time of entrance the diarrhea was marked, there being from eight to ten dejections, containing the usual ingredients of an infectious diarrhea stool, namely, blood, pus and mucus. Her prostration was slight. She had some fever, but she slept fairly well; her appetite was variable.

Physical examination showed that considering the poor way in which she had been nourished in the past, her development and nutrition were fairly good. Her general appearance and color, while not normal, had not the aspects of a serious infection. The anterior fontanel was still open, otherwise the head was normal. Rigidity and retraction of the neck were negative. There were not as yet any of the signs of rickets. The pupils and the eyes in general seemed normal. The tongue was slightly coated and mouth was clean. There were no teeth present. Glandular enlargement was not present. The heart, lungs and liver were negative. The abdomen was somewhat pendulous. The reflexes were diminished. No edema was present. The skin was clear, clean, flaccid and smooth.

Examination of stools made Aug. 15, 1915, showed the presence of *B. welchii* and streptococci.

SUMMARY

Total Leukocyte Counts (Weekly Average)

1. There was a progressive weekly increase in the total leukocyte count.

2. Contrasted with this fact, there was a corresponding fall in the temperature.

3. The range of the leukocyte count was least with Flexner bacillus infection and greatest with the mixed infection.

4. Group 1 is characterized by having a normal leukocyte count at the onset, followed within from two to four days by a marked leukopenia, which persists until the convalescent period, unless there are complications. (The normal blood count is from 9,000 to 11,000 [Hayem] for children between the ages of 6 months and 5 years.) Group 2 is characterized by a rather high leukocyte count throughout the illness. Group 3 shows a marked leukocytosis from the beginning, slightly decreasing toward the middle of the illness, but always showing an increased cell count. If one of the organisms is the typhoid or paratyphoid bacillus, combined with *B. welchii,* then the leukocytosis will be diminished; but, on the other hand, if the *B. welchii* is combined with streptococci, a greater leukocyte count than Group 2 will be noticed.

Differential Counts

Group 1 (Sixteen Cases, B. dysenteriae, Flexner)

1. High neutrophilic count for the first two weeks, with corresponding low, small mononuclear count.
2. Large mononuclears increased throughout.
3. Rarity of eosinophils and basophils.
4. Slight increase in neutrophils and a slight decrease of the small mononuclears for the third and the fourth week.
5. Generally a rise follows a remission of the neutrophils and vice versa for the lymphocytes.
6. Myelocytes were present in five cases.
7. Transitional cells were present, particularly when a toxic element was in evidence.

Group 2 (Five Cases, B. welchii)

1. Slight increase of neutrophils.
2. Absence of eosinophils.

Group 3 (Four Cases, Mixed Infection)

1. A small increase in the neutrophils, and a corresponding decrease in the small mononuclears.

2. The large mononuclears show a greater increase than in the two previous groups.

Average Differential Counts, Groups 1, 2 and 3

(Twenty-Five Cases)

1. Large mononuclears increased throughout.
2. Transitional cells are found in about 30 per cent. of the cases, particularly in Group 1 (severe and mild type).
3. Practical absence of eosinophils and basophils.
4. Presence of the so-called Türck's cell in about 20 per cent. of the cases.
5. Large mononuclears, giant cell types, were seen frequently in about 25 per cent. of the cases. They were, however, but few in number. The nuclei were deeply stained by both Giemsa's and Wright's stains.
6. Small mononuclears, Türck's[32] cells, were present. Schleip called my attention to a cell somewhat larger than the small mononuclear and having in addition more protoplasm and less nucleus.
7. Neutrophils showed in many instances a slight degree of transition, but not sufficient to classify them in this group.
8. Basophils were not present.
9. Eosinophils were present in a small number of cases.
10. Transitional cells were present in cases in which the toxemia was more pronounced.

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[32] My attention was called to these cells while reading a book by Schleip (Footnote 26). Personally, I do not see a sufficient reason for a separate division; these were simply recorded as a matter of interest.

THE SPECIFIC DIAGNOSIS OF TUBERCULOUS MENINGITIS

A PRELIMINARY COMMUNICATION *

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The pathology of the cerebrospinal fluid in cases of tuberculous meningitis has been the object of intense study in recent years. However, the diagnostic value of examinations of that fluid simply by chemical and cytologic methods is of only relative importance. The most reliable test is to find tubercle bacilli in the cerebrospinal fluid; but that is microscopically often so difficult that in most cases no satisfactory result can be obtained. Consequently, the necessity arises of performing animal injections to confirm the diagnosis. But it is well-known that a comparatively long time, even more than three weeks, is required to determine the result of the experiment. For this reason the method has been abandoned. It is also well known that the presence of the tuberculosis organism produces three kinds of reaction to tuberculin injection, namely, (1) general reaction, (2) focal reaction and (3) local reaction. The focal reaction may well be adopted to diagnose tuberculous diseases, but there is no record of an instance of that reaction being used as a diagnosis of tuberculous meningitis. It seems worth while, therefore, to report the following cases, even though they are small in number.

The diagnosis of tuberculous meningitis by the focal reaction of tuberculin is simple but specific in nature. The process is as follows: After taking out a certain quantity of cerebrospinal fluid by lumbar puncture for cytologic examination, an intradural injection of diluted tuberculin (Koch's old tuberculin) is made. After six, twelve or twenty-four hours cytologic examination is again made of the fluid, which is obtained by lumbar puncture, and a comparison is made of the cell count before and after the intradural injection. The dose of tuberculin injected into the spinal canal is from 0.01 to 0.002 mg., with which a satisfactory result can be obtained. In the preparation of the tuberculin it is well to dilute it with physiologic salt solution (from 0.5 to 1 c.c.).

In this way I have examined the cerebrospinal fluids nine times in five cases of tuberculous meningitis, the result of which I have summarized in Table 1.

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* From the Department of Pediatrics of the Medical College, the Kyoto Imperial University.

TABLE 1.—Results of Cerebrospinal Fluid Examination Following Tuberculin Injection in Five Cases of Tuberculous Meningitis

Case No.	Name	Age, Years	Nervous Symptoms	Cerebrospinal Fluid	Dose of Tuberculin, Mg.	Cerebrospinal Fluid After the Intradural Injection of Tuberculin
1	H. O.	3	Nausea; vomiting; tremor; convulsions; stiffness of neck; limbs rigid; Kernig's sign	Slight turbidity; albumin 0.079%; globulin +; lymphocytes 38; polymorphonuclears 118; red cells 60	0.001	After 12 hours: albumin 0.089%; lymphocytes 150; polymorphonuclears 330; red cells 3,200 After 24 hours: albumin 0.089%; lymphocytes 310; polymorphonuclears 215; red cells 585
2	K. Y.	5	Vomiting; apathy; nystagmus; rigidity; Kernig's sign; delirium; stiffness of neck	Turbid: albumin 0.148%; globulin +; lymphocytes 123; polymorphonuclears 40; red cells 0	0.002	After 24 hours: albumin 0.156%; lymphocytes 237; polymorphonuclears 130; red cells 53 After 36 hours: albumin 0.151%; lymphocytes 193; polymorphonuclears 97; red cells 7
3	M. Y.	1	Vomiting; apathy; convulsions; limbs rigid; Kernig's sign; stiffness of neck	Slight turbidity; albumin 0.102%; globulin +; lymphocytes 104; polymorphonuclears 8; red cells 0	0.001	After 6 hours: albumin 0.247%; lymphocytes 190; polymorphonuclears 16; red cells 352
4	S. T.	2	Headache; nausea; vomiting; coma; head retraction; convulsions	Slight turbidity; albumin 0.095%; globulin +; lymphocytes 50; red cells 5	0.001	After 24 hours: albumin 0.165%; lymphocytes 910; polymorphonuclears 525; red cells 395
5	T. M.	1½	Vomiting; stiffness of neck; apathy; convulsions; limbs rigid	Turbid; albumin 0.11%; globulin +; lymphocytes 140; red cells 0	0.01	After 12 hours: lymphocytes 855; polymorphonuclears 46; red cells 193 After 24 hours: lymphocytes 716; polymorphonuclears 9; red cells 100 After 72 hours: lymphocytes 164; polymorphonuclears 0; red cells 10

In the examination of the cerebrospinal fluid attention was paid also to an estimation of the pressure, the number of cells per cubic millimeter, the types of cells and an estimation of the globulin and albumin content. For cytologic examinations the Fuchs-Rosenthal method (modified) was adopted. For estimating the albumin I used the nitric acid ring when it was first formed, while globulin was tested by Noguchi's butyric acid method.

As Table 1 shows, tuberculous meningitis gives specific reactions to the intradural injection of tuberculin; in other words, cytologic examination after tuberculin injection shows an increase in the number of cells in general. Chiefly, there are a remarkable appearance of red cells, a considerable increase in the lymphocytes, and a moderate increase in the polymorphonuclear leukocytes. A large percentage of red cells in the cerebrospinal fluid is a significant phenomenon which needs much attention. It is due to hyperemia owing to the reactive nature of the pia mater. In the case of tuberculous meningitis, the cerebrospinal fluid after the intradural injection is remarkably turbid macroscopically and even yellowish in color occasionally.

For a comparative study I tried the intradural injection of tuberculin (from 0.01 to 0.001 mg.) in children with suppurative meningitis, epidemic cerebrospinal meningitis, and with chronic hydrocephalus, but I saw no change of the cells in the cerebrospinal fluid (Table 2).

TABLE 2.—Results of Cerebrospinal Fluid Examination Following Tuberculin Injection in Cases of Hydrocephalus and Nontuberculous Meningitis

Case No.	Name	Age	Diagnosis	Cerebrospinal Fluid	Dose of Tuberculin, Mg.	Cerebrospinal Fluid After the Intradural Injection of Tuberculin
1	S. H.	11 mo.	Suppurative meningitis	Turbid; albumin 0.462%; globulin +; lymphocytes 1,450; polymorphonuclears 1,765; red cells 15; streptococci present	0.001	After 24 hours: albumin 0.412%; lymphocytes 420; polymorphonuclears 720; red cells 10
2	F. Y.	3 yr.	Chronic hydrocephalus	Clear; colorless; albumin 0.02%; globulin —; lymphocytes 4; polymorphonuclears 0; red cells 10	0.01	After 24 hours: albumin 0.021%; lymphocytes 4; red cells 1
3	S. T.	8 yr.	Epidemic cerebrospinal meningitis	2/24. Turbid; albumin 0.214%; globulin +; lymphocytes 136; polymorphonuclears 1,860; red cells 5,580 meningococci present	0.002	After 24 hours: albumin 0.198%; lymphocytes 130; polymorphonuclears 1,860; red cells 4,800
				3/2. Turbid; albumin 0.132%; globulin +; lymphocytes 142; polymorphonuclears 954; red cells 40	0.002	After 24 hours: albumin 0.0825%; lymphocytes 145; polymorphonuclears 594; red cells 5
				3/7. Turbid; albumin 0.1089%; globulin +; lymphocytes 96; polymorphonuclears 536; red cells 0	0.01	After 24 hours: albumin 0.0297%; lymphocytes 94; polymorphonuclears 500; red cells 0

SUMMARY

The diagnosis of tuberculous meningitis by the intradural injection of tuberculin is specific but very simple. Among specific reactions, the most conspicuous thing is an increase in the cell count of the cerebrospinal fluid, especially that of the red cells.

I may add that as my studies are continued I shall in future have the pleasure of forwarding further reports on this subject.

DIABETES MELLITUS IN CHILDREN

REPORT OF TWO CASES WITH A STUDY OF THE URINARY NITROGEN *

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Frequency.—From time to time reported cases of diabetes in childhood have been collected, the first such collection having been made by Kulz in 1878, and the last by Morse[1] in 1913. There are now on record more than 1,000 cases, in which an equal distribution between boys and girls and an incidence increasing with the age are observed. Though over 100 cases in children under 1 year of age have been reported, there is nothing in the majority to show that the sugar was glucose, and it is quite probable that many of these were cases of lactosuria. Knox,[2] in going over the literature in 1911, could find but 16 cases which he regards as true diabetes. In Morse's collection there are 200 children under 5 years of age, which, considering the time period covered by the survey, makes the disease at this early age almost a rarity. It has been estimated that among diabetics of all ages, the childhood incidence is about 2 per cent.

Prognosis.—The prognosis in children has been regarded by all writers on the subject as grave, no matter how mild in the beginning or how gradual in development. Among the collected cases there are twenty-six patients reported as recovered, but the proof of recovery is satisfactory in less than ten, one third of the cases having been followed but three months or less. On the basis of ten recoveries in one thousand cases there has been a mortality of 99 per cent.

The Allen Treatment.[3]—No one can say what is now the ultimate prognosis of diabetes in childhood under the new régime which more than vaguely promises a long life of good health if not a permanent cure. There are no case reports of children under this new régime to show even its immediate effects. Since the publication of Allen's work there have come under our observation two cases of diabetes mellitus in childhood which will be reported in detail.

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* Submitted for publication Dec. 10, 1916.

* From the Department of Pediatrics, Washington University Medical School, and St. Louis Children's Hospital.

[1] Morse, J. L.: Boston Med. and Surg. Jour., 1913, **168,** 530.

[2] Knox, J. H. Mason, Jr.: Bull. Johns Hopkins Hosp., 1913, **24,** 274.

[3] Allen, F. M.: Studies Concerning Glycosuria and Diabetes, Harvard Univ. Press, Cambridge, Mass., 1913; ibid., Jour. Am. Med. Assn., 1914, **58,** 539; ibid., Boston Med. and Surg. Jour., 1915, **172,** 241; ibid., Am. Jour. Med. Sc., 1915, **150,** 480; ibid., Boston Med. and Surg. Jour., 1915, **173,** 743.

REPORT OF CASES

Case 1.—The patient was a girl 2 years of age.

Family History.—The father, mother and one older child are all in good health and there is no history of diabetes in the family.

Past History.—The patient was born spontaneously at term, was breast fed, and developed normally both mentally and physically. There has been no illness except as is mentioned below.

Present Illness.—The patient first came under observation Dec. 30, 1914, for frequency of urination, which had been present for three weeks following an intestinal disturbance. She received treatment for this condition for one month, with improvement. During this month of observation she gained in weight from 11.15 to 11.94 kg. and three urine examinations showed nothing abnormal. She again came under observation May 11, 1915, with the history of having had measles during the latter part of March, with which she had been very ill for three weeks. The urine was not excessive or troublesome before the measles, but did become so immediately afterward. At this time the mother noticed that the diapers were sticky, and a few days later sugar was found in the urine by the family physician. The polyuria was associated with greatly increased thirst, demanding water numerous times during the night. Sleep was broken and restless. When obtained on May 11, the urine caused abundant reduction of Fehling's solution and fermented with yeast. The child was admitted to the St. Louis Children's Hospital May 22, 1915, at which time the general physical examination revealed nothing of importance. She was exceedingly well nourished and did not appear ill, though she was irritable and had general malaise. The Wassermann reaction was negative. Her weight on admission to the hospital was 11.6 kg. and her age was 26 months.

Progress.—On the regular hospital diet the patient excreted 46 gm. of sugar in twenty-four hours. With the institution of fast she became sugar-free in the first twenty-four hours and at the same time her increased thirst disappeared and the amount of urine decreased abruptly from 1,500 c.c. daily to 700 c.c., and later to much less than this. She slept well at night and her general disposition improved. With a gradual increase in the diet over a period of three weeks, she showed glycosuria on a diet having a value of 870 calories and including 22 gm. of carbohydrate. Following another fast day she remained sugar-free on various diets (Table 1) until she was discharged from the hospital, Nov. 24, 1915. The successful handling of several of these diets indicates an increase in her tolerance. Her diet at home was practically a constant one and she remained sugar-free and in good health for a month, when she returned with an acute bronchitis and a slight glycosuria. The bronchitis was rather severe and there was considerable fever for three days. On readmission to the hospital, Dec. 17, 1915, she received, by mistake, a diet slightly in excess of the previous allowance, and yet the urine became sugar-free, with improvement of the acute infection. She was discharged December 24 with a lower diet. The urine was examined almost daily and sugar was found on March 8 and March 14, 1916. She had been having a carbohydrate free diet one day each week. The patient was readmitted to the hospital March 15, 1916, when she was again fasted and discharged with a lower diet. She remained sugar-free and free from complaints until Nov. 7, 1916, when, associated with a slight indigestion and a coryza, she again had a small amount of sugar in the urine. She is now sugar-free and in good health. Her weight in November, 1916, was 13.6 kg.

Discussion of Case 1.—The criteria of the condition of a diabetic are the amount of sugar in the urine and blood and the degree of acidosis. The degree of acidosis may be measured in a variety of ways, but the common methods, and the ones used in these cases, are the amounts of acetone bodies excreted in the urine and the urinary ammonia coefficient. At no time was the acidosis of such a degree as to give distinct clinical manifestations, though during all observation periods the amount of acetone bodies in the urine was definitely increased above the normal. During the last period the amounts were strikingly less than before. Following each fasting period there occurred a marked increase in the acetone bodies, which made but a short curve, quickly returning to a lower level as food was allowed. This increase was rather to be expected, but the decrease which occurred in every instance on the day of fast seemed unusual and is in distinct contrast to the behavior of the normal child. This phenomenon might be the object of considerable speculation, though the most plausible explanation would seem to be the sudden withdrawal of protein with its acetone body precursors, together with the availability of stored glycogen in sufficient amounts to protect the normal combustion of fats. As the stored glycogen decreases, there occurs an increase in acetone bodies, as in any other patient. The more acetone body formation is studied the more complicated does the question become, and whether or not this phenomenon is to be explained in this way, the fact itself is of interest.

The ammonia followed the acetone curve fairly closely, though it seemed somewhat delayed in excretion. At all times the ammonia coefficient was found increased over that found in normal children. During the last period the ammonia, as well as the acetone bodies, was lower than in previous periods, which is encouraging in the prognosis for this patient.

The values given in the accompanying tables for blood sugar are lower than other published observations, probably due to the method employed. The method followed was that of Shaffer,[4] who, in his paper, discusses the difference in results by his method and by previously published methods. Whatever criticism may be directed against any method in current use as being an absolute measure of blood sugar, still leaves that method of value in determining comparative results. To determine the normal value by this method a number of presumably normal children from 2 to 3 years of age were selected and blood samples were taken after a night of fast and before breakfast. The normal values thus obtained varied closely in the neighborhood of 0.05 per cent. If the sample was taken later in the day, after food had been given, the values were higher. The figures in the accompanying tables represent the morning fasting values.

Relatively few observations have been made of the blood sugar in this patient, but there is a sufficient number to show that there has

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[4] Shaffer, P. A.: Jour. Biol. Chem., 1914, **19,** 285.

TABLE 1.—DATA—

Date, 1915	Diet				Calories		Weight, Kilos
	Fat	Protein	Carbo-hydrate	Alcohol	Total	Per Kilo	
May 25*	..	..	..	..	.....	..	.....
27	65	34	27	0	855	73	11.66
28	65	34	27	0	855	73	.....
31	87	42	30	0	1,110	97	11.38
June 1	87	42	30	0	1,110	97	.....
2	0	0	0	25	175	15	.....
3	21	5	0	0	215	20	.....
4	43	14	4	7	520	47	.....
5	41	19	13	9	575	53	10.83
7	54	25	13	9	720	68	10.63
9	54	25	13	9	720	68	10.60
11	54	25	13	9	720	66	10.91
12	54	25	13	9	720	65	11.08
15	64	32	13	9	840	78	10.86
18	68	35	18	4	880	81	10.89
21	72	39	22	0	870	78	11.14
23	0	0	0	25	175	16	11.14
24	17	4	0	16	285	26	10.89
26	51	21	13	13	705	67	10.52
28	55	20	16	11	735	71	10.40
30	66	25	13	11	850	80	10.69
July 2	76	32	13	9	950	89	10.66
5	76	32	13	9	950	87	10.89
9	76	32	13	9	950	88	10.86
16	76	32	13	9	950	88	10.77
20	76	32	13	9	950	85	11.14
23	76	32	13	9	950	85	11.25
27	76	32	13	9	950	87	10.97
Aug. 5	76	32	13	9	950	87	11.00
7	80	35	18	4	995	90	11.05
12	84	39	22	4	1,060	93	11.43
Sept. 8	84	39	22	4	1,060	91	11.66
20	84	39	22	4	1,060	89	11.96
28	76	29	27	4	965	81	11.99
Oct. 9	76	29	27	4	965	80	12.04
11‡	80	35	18	0	970	85	11.43
21	80	35	18	0	970	81	11.99
29	80	35	18	0	970	80	12.07

* Hospital diet.

† The heading "Acetone" includes diacetic acid. Beta-oxybutyric acid is recorded as acetone.

‡ Oct. 10, 1915, was a fast day.

—of Case 1

Blood Sugar, per Cent.	Urine				Urinary Nitrogen				
	Amount, C.c.	Sugar, Gm.	Acetone,† Mg.	B.-oxy-butyric, Mg.	Total N, Gm.	Ammonia N, Mg.	Creatinin N, Mg.	Creatin N, Mg.	Uric Acid N, Mg.
.....	1,020	46							
.....	1,480	14	...	.....	5.01	1,080	55	..	49
.....	1,490	14	...	.....	5.40	930	53		
.....	1,300	23	487	1,157	5.41	820	46	39	63
.....	1,485	27	438	1,276	4.48	850	47	45	38
.....	700	0	...	.....	2.49	300	36	..	40
.....	715	0	240	1,024	1.93	300	28	38	25
.....	765	0	360	1,590	2.63	500	37	38	53
0.045	880	0	310	1,440	3.26	600	36	46	45
.....	935	0	140	430	3.34	600	34	39	38
.....	715	0	120	140	2.24	300	25	35	43
.....	705	0	200	230	3.21	410	32	42	51
.....	555	0	60	140	1.85	200	27	29	38
.....	555	0	160	620	2.36	360	28	35	41
0.057	580	0	160	670	4.10	670	38	42	65
0.088	675	1	287	590	4.59	370	52	57	59
.....	875	0	87	160	2.52	480	47	49	50
0.030	625	0	350	2,300	2.72	510	41	72	29
.....	520	0	320	1,320	2.14	620	34	38	60
0.047	735	0	220	770	2.68	770	41	39	49
.....	545	0	106	300	1.88	354	31	32	35
.....	495	0	131	463	3.09	390	31	41	45
.....	605	0	188	658	2.84	418	27	48	45
.....	510	0	125	378	2.91	304	..	..	44
.....	375	0	454	1,040	2.65	.....	43	55	54
.....	525	0	131	361	3.05	367	32	49	41
.....	410	0	227	439	2.20	340	25	34	21
.....	390	0	226	480	2.60	557	36	39	31
.....	660	0	545	1,240	3.20	702	33	38	32
.....	550	0	...	.....	2.54	495	34	..	38
.....	525	0	131	400	2.40	327	31	..	35
.....	400	0	180	870	2.63	567	41	32	
.....	500	0	110	423	3.01	387	37	52	33
.....	610	0	137	200	3.77	423	49	67	47
0.061	330	0	201	975	2.40	293	35	46	40
.....	460	0	722	2,400	4.09	968	46	79	68
.....	295	0	94	280	2.95	300	28	41	32
.....	350	0	222	890	2.25	287	32	49	37

TABLE 1.—DATA OF—

Date, 1915	Diet				Calories		Weight, Kilos
	Fat	Protein	Carbohydrate	Alcohol	Total	Per Kilo	
Nov. 19	80	35	18	0	970	78	12.48
Dec. 18	84	39	22	26	1,235	..	.....
20	84	39	22	26	1,235	100	12.39
21	0	0	0	25	175	14	12.24
23	84	34	13	0	980	80	12.28
1916 Mar. 16	80	35	18	0	965	73	13.14
17	0	0	0	25	175	..	.....
18	65	20	20	0	765	..	.....
19	65	20	20	0	765	59	13.05
21	65	20	30	0	810	62	13.14
22	65	20	40	0	850	65	13.14
23	65	20	50	0	890	68	13.17
24	65	20	60	0	930	70	13.22
25	0	0	0	25	175	13	13.25
26	35	13	10	0	420	..	.....
27	65	20	20	0	770	59	12.94

TABLE 2.—DATA—

Date, 1915	Diet				Calories		Weight, Kilos
	Fat	Protein	Carbohydrate	Alcohol	Total	Per Kilo	
Nov. 25*	..	..	..	..	.....	..	.....
27	69	38	31	0	925	56	16.14
28	69	38	31	0	925	..	.....
Dec. 1	77	45	40	0	1,065	67	15.91
2	81	48	45	0	1,135	71	15.91
3	81	48	55	0	1,175	73	16.19
4	81	48	65	0	1,215	74	16.39
5	81	48	75	0	1,255	76	.....
6	0	0	0	24	170	10	16.00
7	13	3	0	6	175	11	15.70
8	55	20	16	9	675	44	15.43
10	66	26	13	9	835	53	15.67
12	76	32	13	9	955	61	15.64
14	80	36	18	0	965	61	15.75
17	84	39	22	0	1,035	66	15.72
20	84	41	22	0	1,040	67	15.61

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* Hospital diet.

† The heading "Acetone" includes diacetic acid. Beta-oxybutyric acid is recorded as acetone.

‡ The blood sugar is charted opposite the diet which it represents. The determination was made the day following.

—Case 1—(*Continued*)

Blood Sugar, per Cent.	Urine				Urinary Nitrogen					
	Amount, C.c.	Sugar, Gm.	Acetone,† Mg.	B.-oxy-butyric, Mg.	Total N, Gm.	Ammonia N, Mg.	Creatinin N, Mg.	Creatin N, Mg.	Uric Acid N, Mg.	Urea N, Gm.
0.054	430	0	267	895	3.37	537	44	60	31	
.....	345	2	400	1,350						
.....	340	0	272	650	3.88	467	40	57	50	
0.089	375	0	160	574	2.14	234	39	45	34	
.....	250	0	557	884	2.92	610	32	50	64	
0.071	850	0	520	2,090	4.55	589	48	72	28	3.35
.....	500	0	95	234	2.49	413	41	64	47	1.53
0.041	345	0	46	1,610	3.82	700	43	73	46	2.45
.....	300	0	353	1,160	3.31	667	39	52	52	1.92
.....	325	0	85	103	3.07	431	44	53	77	2.01
.....	210	0	70	149	2.48	266	45	53	58	1.73
.....	355	0	50	55	2.24	200	43	58	58	1.52
.....	380	0	52	50	2.27	194	45	55	54	
0.060	315	0	24	35	1.73	156	41	46	41	
.....	345	0	98	214	2.76	251	50	67	53	
.....	525	0	180	440	2.50	309	42	49	43	

—of Case 2

Blood Sugar,‡ per Cent.	Urine				Urinary Nitrogen				
	Amount, C.c.	Sugar, Gm.	Acetone,† Mg.	B.-oxy-butyric, Mg.	Total N, Gm.	Ammonia N, Mg.	Creatinin N, Mg.	Creatin N, Mg.	Uric Acid N, Mg.
.....	810	40	255	846	6.30	494	126	208	93
.....	535	0	410	1,720	5.92	571	81	130	84
0.057	660	0	235	709	6.76	870	84	117	131
0.053	705	0	220	16	5.92	422	77	55	95
.....	665	0	145	88	5.99	395	70	61	108
0.062	565	0	80	71	6.06	349	86	55	99
0.074	860	0	70	55	6.80	379	98	59	102
0.063	605	1	45	22	4.78	277	59	61	82
0.034	805	0	280	66	5.03	251	86	47	90
0.035	430	0	219	900	4.21	255	48	95	48
0.059	455	0	420	2,400	4.44	454	67	87	72
0.049	500	0	154	242	....	293	65	..	60
.....	650	0	205	431	4.41	474	57	50	58
0.058	655	0	108	270	4.03	377	71	32	64
0.052	490	0	81	157	5.88	471	..	27	77
0.050	350	0	153	272	3.60	235	64	29	33

been at no time after starting treatment a very marked hyperglycemia. It is generally stated that the blood sugar of normal individuals does not decrease appreciably below the normal level with a short fast, and such also has been our experience. It is stated, also, that a high blood sugar in diabetes is not lowered as quickly as in normal subjects, though a subnormal drop in blood sugar following fast is very noticeable in this patient.

At the beginning of observation this patient had an average body weight for her age, 11.6 kg. During the first year of observation there was a gain of 1.4 kg., and during the first six months of the second year there has been a gain of 0.6 kg. There has been a considerable increase in her body length, and it is evident that her growth has been at the expense of her stores of body fat. She is now below the average weight for her age.

Summary of Case 1.—A moderately severe case of diabetes mellitus in a 2-year-old girl, coming under observation early and remaining under observation one and one-half years, was made sugar-free by an initial fast, and remained sugar-free throughout the observation period except for five occasions. One of these was due to intentional overfeeding, and another was the result of an acute infection. The other three occasions were transient and occurred only on the days mentioned. There has been complete relief of the subjective symptoms and the polyuria, and there is considerable evidence that her tolerance has increased. At no time was the evidence of acidosis sufficient to draw any especial attention to it. Though she is by no means cured, there seems to be no good reason why she should not have a long life, free from diabetic symptoms.

CASE 2.—The patient was a boy aged 3 years.

Family History.—The father and mother and the child of the first pregnancy are in good health. A Wassermann reaction on the mother was negative. The second and fourth pregnancies resulted in miscarriage. The fifth pregnancy resulted in a premature birth at six and one-half months, the child of which died of bronchopneumonia at 9 months.

Past History.—The patient was the child of the third pregnancy and was delivered by means of forceps at term. He was normal at birth and continued so for several months. From the age of 6 months he was frequently brought to the Children's Hospital dispensary for various minor ailments. During infancy he was an overfed, condensed milk baby, fat, but having recurring attacks of diarrhea, with one of which at 21 months he had two convulsions. Condensed milk was continued both with this baby and the succeeding one, contrary to all advice, which illustrates the parental attitude to our instruction. The patient cut his teeth, walked and talked at the usual age. There was an acute bronchitis at 18 months and again at 2 years. Aug. 16, 1915, he became ill with measles, which ran a mild course.

Present Illness.—He was admitted to the Children's Hospital, Nov. 25, 1915, having had polyuria and increased thirst for two weeks. These symptoms were associated with loss of appetite, slight loss of weight and a definite bread hunger. There were no other complaints.

Examination.—The patient was well nourished and apparently in good health. There were several features that suggested dyspituitarism. The hands were spade-like and the skin was dry. The fingers were of the shape seen in acromegalics. The hands and feet were large and the stature was somewhat above the normal. Roentgenograms of the sella turcica and of the feet and hands showed no abnormalities.

Progress.—On the regular hospital diet the patient excreted 40 gm. of sugar in twenty-four hours. On restricted diet without fast he became sugar-free in the first twenty-four hours, and with a gradual increase in the diet he again had glycosuria when the diet reached the value of 76 calories per kilogram and included 75 gm. of carbohydrate. Following a fast he became sugar-free and remained so on his subsequent diet until April 3, 1916, a period of four months. After this time the parents refused to keep him under supervision and the dietary restrictions were largely removed. He is said to have remained in good health until June 1, 1916, when he became ill. June 2 he was admitted to the Children's Hospital in coma. At this time he had deep, pauseless respirations at the rate of 52 per minute, his temperature was 102.4 F., and there were râles at the bases of both lungs. Following the intravenous administration of 150 c.c. of 4 per cent. sodium bicarbonate solution, the respiratory rate decreased to 36, the patient recognized his mother and held simple conversation. Four hours later he was again comatose and the respiratory rate was 70. Following intravenous administration of sodium bicarbonate he became more quiet at once, and at no time later did he show air-hunger breathing. The urine for twenty-four hours, from June 2 to 3, measured 100 c.c., and showed much albumin and many casts. There was no sugar. The ammonia nitrogen was 24 per cent. of the total nitrogen. The urine for twenty hours from June 3 to 4 measured 465 c.c. and showed much albumin and many casts. There was 1.2 gm. sugar and the ammonia nitrogen was 12 per cent. of the total nitrogen. Examination of the blood on June 3 showed, per 100 c.c., 103 mg. of nonprotein nitrogen, 38 mg. of acetone and diacetic acid and 75 mg. of beta-oxybutyric acid (as acetone). The blood sugar was 0.3 per cent. The blood on June 4 showed, per 100 c.c., 41 mg. acetone and diacetic acid and 107 mg. beta-oxybutyric acid (as acetone). The blood sugar was 0.4 per cent. The white cell count on June 3 was 60,000, of which 70 per cent. were polymorphonuclear cells. Death occurred on June 4, being preceded by several clonic convulsions. A necropsy was refused.

Discussion of Case 2.—When this patient first came under observation there was some question as to whether the case was one of true diabetes or a transient glycosuria. Though he had a high tolerance for carbohydrate, there was considerable evidence in favor of the diagnosis of diabetes. There was at all periods except one a distinct tendency toward acidosis, as shown by the laboratory findings. In the twenty-four-hour period which makes the exception he received 75 gm. of carbohydrate and showed a glycosuria. He showed a hyperglycemia while receiving from 55 to 75 gm. of carbohydrate in twenty-four hours, and a fairly marked subnormal drop in blood sugar following fast. The twenty-four-hour amount of urine was not excessive, but he was removed from the regular hospital diet and routine so quickly after admission that this point was not well determined. There was a definite polyuria before admission. The thirst and polyuria quickly disappeared under treatment, but the bread hunger remained.

The marked increase in the acetone bodies on the day of fast differs from Case 1 and corresponds to the normal child. Otherwise the figures for the acetone bodies and for ammonia are similar in kind though not in degree to those of Case 1.

Up to April, 1916, at which time his visits ceased, the prognosis seemed good. As Allen states, there are two factors which determine the success of treatment, the scientific and the human factor. In Case 1 the human factor is found at its best, while in Case 2 this factor was apparently the point of failure, this being by far the milder of the two cases. The scientific factor was the same in both instances.

Aside from possible pneumonia, there is evidence that the death of this patient was due to two factors, acidosis and uremia. When observed in April the urine was free from albumin, but previous to his death both the urine and the blood showed evidence of a nephritis with retention of nonprotein nitrogen. The alkali therapy relieved the acidosis to some extent, but had little effect on prolonging his life.

Summary of Case 2.—A mild case of diabetes in a 3-year-old boy coming under observation two weeks after the onset of symptoms. Merely lowering the diet was sufficient to make the urine sugar-free. There was relief of the polyuria and subjective symptoms, except bread hunger, by regulation of the diet. He remained sugar-free and in good health during the four months of observation. Following this the dietary restrictions were broken and death occurred six and one half months after the onset from acidosis and uremia.

Diet.—In spite of Allen's statement that we should be governed by no theoretical standards of calories or protein, but rather by the individual tolerance for each individual food, it is well to have in mind the theoretical considerations that go to make up a well-balanced diet. If the patient's tolerance permits, it would seem better for him to have a well-balanced than a badly balanced diet, and the younger the patient the more important does this become. The protein needs of a child are about 1.5 gm. per kilogram, and this amount constitutes from 9 to 13 per cent. of the total calories. As to the proportion of fat and carbohydrate that should make up the diet, there are no absolute data. Though the diet of a thriving child varies within rather wide limits in different individuals, one, the food value of which beside the protein is equally distributed between the fats and carbohydrates, makes a very good average. Fats and carbohydrates are of almost equal importance as protein sparers. It seems likely that in the young, growing child the body needs are best supplied by having the food value of the fats somewhat greater than that of the carbohydrates, even as much as 25 per cent. greater. In preparing a restricted or minimum diet for a child there should be at least the minimum requirement of protein, 1.5 gm. per kilogram, the fats should be about 50 per cent. and the carbohydrates about 40 per cent. of the total calories. In many diabetic children this amount of carbohydrate would not be well tolerated, and for this reason it should be decreased and the fat increased sufficiently to meet the needs of the individual patient.

Body Weight.—The question of diet has a very intimate relation to that of body weight. Allen's statement that any increase in body weight that is attended with glycosuria or an increase in the acetone bodies should be checked holds true for children as well as for adults, but apparently little attention is paid to the fact that children are expected to grow. This growth must ultimately involve increase in weight, and it would seem necessary to allow a reasonable increase in weight in any child who remained sugar-free and acetone-free.

NITROGEN DISTRIBUTION IN THE URINE

A study of the urinary nitrogen was made in the two cases of this report, extending over a period of ten months in Case 1, and of one month in Case 2. The total nitrogen, creatin, creatinin, uric acid and ammonia were determined, and in Case 1 the urea was determined during one period.

Creatin and Creatinin.—For the determinations of this report the revised Folin[5] method was employed. No attempt was made to remove the acetone bodies, since in but few, if any, specimens were these substances present in amounts sufficient to interfere with the determination.[6] The diet was at all times such as is usually termed creatin-free and creatinin-free, and consisted of milk, eggs, butter, cream, and, for most of the periods, vegetables.

Since it has been shown that on a creatin-free and creatinin-free diet the excretion of creatin and creatinin is unaffected by the variety or amount of exogenous protein, except as sugar may be obtained from the protein,[7] a diabetic who is sugar-free and therefore utilizing all of the carbohydrate of the diet might be considered as a normal individual as far as creatin and creatinin excretion is concerned, provided sufficient carbohydrate is fed. There is considerable evidence that, in regard to the excretion of these substances, these patients behaved as normal children. At periods in which relatively large amounts of carbohydrate were allowed and apparently utilized, the creatin and creatinin coefficient was not different from that obtained during periods of lower carbohydrate intake. In Case 1 a slightly higher coefficient was obtained in the later than in the earlier periods, probably because of the relative decrease in adipose and increase in muscular tissue. Taking 12 kg. as the mean weight for the year in Case 1, the average creatin value as 0.048 gm. and the average creatinin value as 0.037 gm., the coefficient is found to be 4 for creatin, 3.1 for creatinin and 7.1 for their sum. In Case 2 is found a coefficient of 3.2 for creatin, 4.6 for creatinin and 7.8 for their sum. This difference in the total coefficients can easily be accounted for by the relatively larger amount of adipose tissue in Case 1. Several normal children[8] of about the same age while having a creatin-free and creatinin-free diet were found to have a total coefficient of from 7.0 to 7.7, with one exception, which gave a coefficient of 10.

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[5] Folin, O.: Jour. Biol. Chem., 1914, **17,** 469.

[6] Greenwald, I.: Jour. Biol. Chem., 1912-1913, **14,** 87. Graham, G., and Poulton, E. P.: Proc. Roy. Soc., Series B, 1914, **87,** 205.

[7] Benedict, S. R., and Osterberg, E.: Jour. Biol. Chem., 1914, **18,** 195.

The coefficients of the total creatin and creatinin nitrogen in these patients is practically the same as is found in adults for creatinin nitrogen,[9] a fact not especially surprising. In adults there is a constant daily and even hourly excretion of creatinin for each individual, though varying somewhat in different individuals. One might expect to find this same constancy for children, if not in creatinin, perhaps in the sum of creatin and creatinin. This has never been shown and does not appear in these patients, though the variations in the amounts of these substances found is not remarkable. Every effort was made to obtain exact twenty-four hour specimens.

Uric Acid.—For all periods up to March 17 there was in the diet of Case 1 a small and fairly constant amount of vegetables, consisting largely of spinach and cauliflower, boiled with three changes of water. Otherwise the diet was purin-free. For the last period vegetables were omitted and the diet consisted of cream, eggs and butter. Benedict's modification of Folin's method of determination was employed.[10] At no time was the uric acid excretion very constant nor was there any constant relation to the total nitrogen. However, the variations were within fairly narrow limits. The average daily excretion of uric acid nitrogen for the periods containing some vegetables was 0.043 gm., and for the period of purin-free diet it was 0.050 gm. In Case 2 there were much higher uric acid values, but these can easily be interpreted as partly exogenous. The patient was removed from a generous diet on admission to the hospital and the uric acid excretion during observation, though irregular, showed a decided tendency to decrease. In a small group of normal children[8] from 18 to 24 months of age, whose previous diet had always been low in purins, the average values for uric acid nitrogen on a purin-free diet was found to vary from 0.051

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[8] These figures were taken from the determinations made by Veeder and Johnston, which are not yet published.

[9] Shaffer, P. A.: Am. Jour. Physiol., 1908, **23**, 1.

[10] Benedict, S. R., and Hitchcock, E. H.: Jour. Biol. Chem., 1915, **20**, 619.

to 0.055 gm. Children older than this who have been accustomed to meat and other purin-containing foods gave even higher values during short interval observations.

The figures here presented show that the uric acid excretion in the two diabetic patients is practically the same as is found in normal children of the same age under similar dietary conditions, and further show the surprising fact that a child of 12 kg. excretes as much uric acid as an adult.[11]

Urea.—In Case 1 urea nitrogen was determined in the last period, the findings not being remarkable in any way. The amounts found varied from 58 to 74 per cent. of the total nitrogen and showed an inverse proportion to the amounts of ammonia present. In the normal child the ammonia nitrogen varies in the neighborhood of 4 to 6 per cent. of the total nitrogen, and the urea 80 per cent. or more. The increased ammonia values during this period account adequately for the decreased urea.

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[11] Raiziss, Dubin and Ringer: Jour. Biol. Chem., 1914, **19,** 473.

SYPHILITIC DISEASE OF THE THYMUS IN INFANTS AND THE MODE OF ORIGIN OF THE DUBOIS ABSCESSES *

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Though first described by Cruveilhier[1] in 1829, cysts in the thymus of the new-born were first carefully studied by Dubois[2] twenty-one years later. By this author they were considered abscesses, on account of their purulent contents, and as all of his cases were in infants who showed definite evidences of congenital syphilis, he regarded the condition as of syphilitic origin.

In the following years of gross pathology numerous cases of "abscesses" of the thymus were described, but it was not until the microscopic study of Chiari[3] that the true nature of these structures became known. In a male infant which died a few minutes after birth and which showed pronounced syphilitic lesions (pneumonia alba, hepatitis, pancreatitis, and osteochondritis syphilitica), he found the thymus, which was not enlarged, to be filled with cavities which contained purulent material. Microscopically, however, these cavities proved to be not abscesses, but cystic spaces lined with a definite epithelial covering of a flat stratified type. As there was a marked cystic dilatation of the Hassall bodies, which were filled with leukocytes, Chiari described the larger cysts as arising from these structures by a process of degeneration and ingrowth of small thymic lymphocytes.

Since this time all authors have agreed on the cystic nature of the cavities, while various views as to their mode of origin and significance in regard to syphilis have been held. The small number of true cystic thymuses found since the introduction of the microscope is due to the exclusion of cases of cavitation in the organ due to postmortem changes. Since Chiari's description, I have been able to find but eight cases of true cystic thymuses in infants.

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* From the Pathological Laboratory of the Medical School of Leland Stanford Junior University.

[1] Cruveilhier, J.: Anat. Path. du Corps Humain, 1829-1835, Book 15, pl. 2. Obs. 6.

[2] Dubois, P.: Du diagnostic de la syphilis considérée comme une des causes possibles de la mort du foetus, Gaz. méd. de Paris, Series 3, 1850, **5**, 392.

[3] Chiari, H.: Ueber Cystenbildung in der menschlichen Thymus, Zugleich ein Beitrag zur Lehre von den "Dubois'schen Abscessen," Ztschr. f. Heilk., 1894, **15**, 403.

Schlesinger,[4] in describing the syphilitic lesions found in the thymus, describes one case of a female child that died shortly after birth, in which cysts were present. In detail the findings and conclusions are almost identical with those of Chiari. Tuve[5] has described two cases of cystic thymus in congenitally syphilitic children. Their origin is explained in a somewhat different manner. According to this author there has been a widespread necrosis of the thymic medulla, due to a failure of development of the blood vessels. The persisting reticulum cells have proliferated and formed the epithelial covering of the cyst.

The most detailed study of such cases has been made by Simmonds.[6] Out of 120 thymuses, the author found two which contained large numbers of cysts. In both, spirochetes could be found in the contents of the cysts and in the cyst walls. Another appearance which Simmonds emphasizes is the relative preponderance of the reticular epithelial cells over the small thymic cells. The Hassall bodies were few in number and the whole organ filled with cysts. Three other thymuses from syphilitic infants showed no cysts, but many Hassall bodies and the same preponderance of reticulum cells over the lymphocytes. The author does not believe that the cysts arise from the Hassall bodies, but that there has been a defective development, with syphilis as the causative factor. The failure of development is shown by the undifferentiated appearance of the thymus (preponderance of epithelial cells) and the cysts, which he identifies with the original cavity of the early thymus.

Pappenheimer[7] in his study of the pathology of the thymus describes two specimens from syphilitic infants. One, a 7-months' macerated fetus, contained cysts; their size is not given. The specimen showed a marked preponderance of the reticulum and disappearance of the lymphocytes. Spirochetes could be demonstrated, and there was a marked increase in the perilobular connective tissue. The author says, "the effect of the congenital syphilitic infection in this case at least is not merely an arrest of development, but an actual atrophy or degeneration of the gland with replacement fibrosis." Another case of congenital syphilis showed no cysts or Hassall bodies, but consisted almost entirely of reticular epithelial cells and a few lymphocytes.

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[4] Schlesinger, E.: Die Erkrankung der Thymusdrüse bei der hereditären Syphilis, Arch. f. Kinderh., 1899, **26,** 205.

[5] Tuve: Ueber die sogenannten Dubois'schen Thymusabscessen, Diss., Leipzig, 1904. (Cited from Simmonds, Note 6.)

[6] Simmonds, M.: Die Thymus bei kongenitaler Syphilis, Virchows Arch. f. path. Anat., 1908, **194,** Suppl., 213.

[7] Pappenheimer, A.: A Contribution to the Normal and Pathological Histology of the Thymus Gland, Jour. Med. Research, 1910, **22,** 1.

The most recent case is that described by Ribbert.[8] A stillborn infant, showing marked evidence of congenital syphilis, had a thymus of normal size, so filled with cysts that on cutting into it, it collapsed. The cysts were lined with a stratified epithelium similar to that of the pharynx, outside of which was a layer of connective tissue, and exteriorly a layer of lymphocytes, arranged in what might be considered follicles. Ribbert concludes that there can be no question of these cysts arising from the Hassall bodies, but that the similarity of its structure to that of the tonsil shows it to be the primary lumen of the developing thymus which has become cystic.

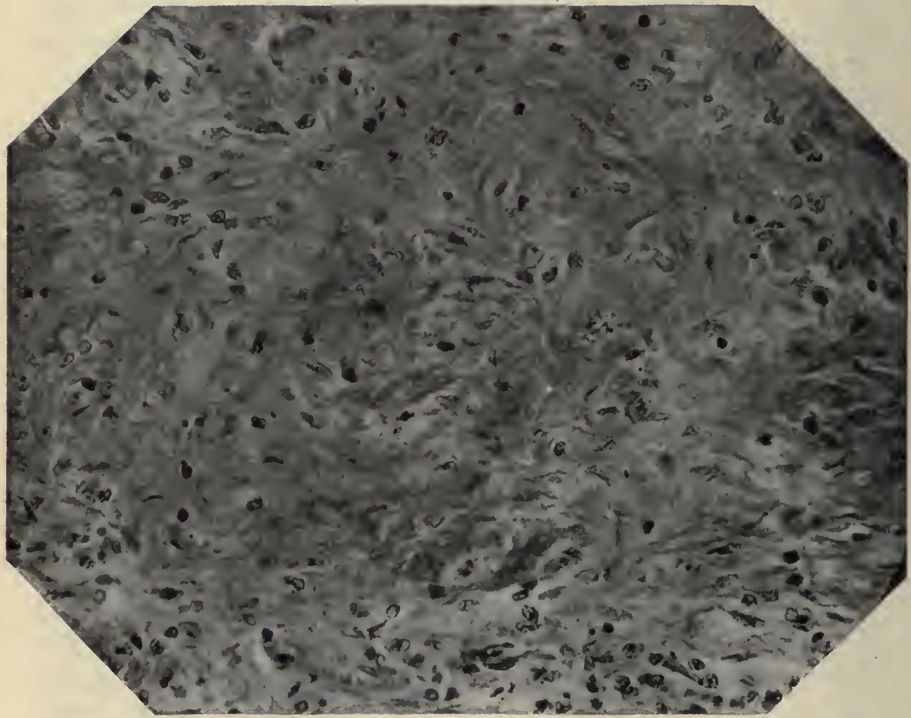

Fig. 1.—Field from the center of a lobule. Nothing remains of the thymus tissue but the shrunken reticulum cells and a few lymphocytes. The main mass of tissue is composed of dense fibrous connective tissue. B. & L. Oc. 1. Obj. ⅙ in.

In reviewing the cases which have been described, we see that all the infants have suffered from congenital syphilis. The cystic nature of the cavities is agreed to by all authors, but the manner of origin is differently described. Chiari and Schlesinger derive them from the Hassall bodies, Simmonds and Ribbert identify them with the primary cavity of the developing thymus, while Tuve holds that they arise by a necrosis of the medullary tissue. Another point of interest is the change seen in the thymus tissue as a whole, which has been pointed out especially by Simmonds and Pappenheimer.

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[8] Ribbert, H.: Die Entwicklungsstörung der Thymusdrüse bei kongenitaler Lues, Frankfurt Ztschr. f. Path., 1912, **11,** 209.

REPORT OF CASE

My case is of interest, not only because of the rarity of the disease, but also from the fact that as the process has not gone on to an extreme degree, the manner of origin of the cysts is plainly seen.

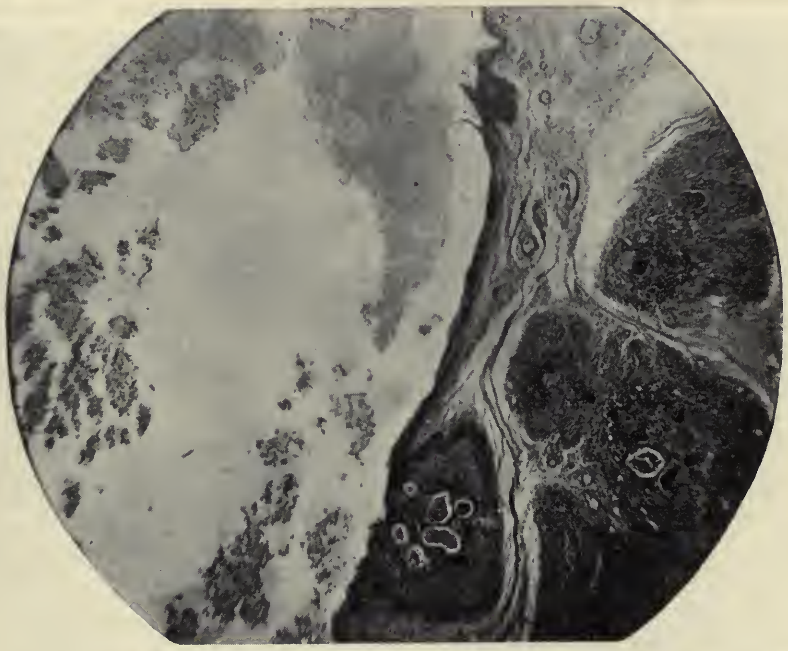

Fig. 2.—A part of the largest cyst with its contents of detritus. Along the margin of the cyst is seen the dark band of the lining epithelium, the remnant of the lobule. At the lower border of the figure, the remnant of thymus tissue is considerably thicker and contains some dilated Hassall bodies. The small dark spots in the other lobules show Hassall bodies of normal size. In the upper part of the section note the remnants of a Hassall body which has ruptured into the main cyst. B. & L. Oc. 1. Obj. 1 in.

History.—An Italian girl baby, 6 weeks of age, was brought to Lane Hospital complaining of fever, discharge from the nose and "blisters" on the abdomen. On examination two large blebs were found on the abdomen, rhagades at the mouth, a serosanguineous discharge from the nose, and edema of the hands and wrists. The urine showed a heavy cloud of albumin, many granular casts, and a few red blood cells. Though no syphilitic history could be obtained from the parents, the baby's Wassermann proved positive. The child was placed on mercurial treatment, but five days after admission died with signs of pneumonia.

Necropsy.—At necropsy, without giving the detailed descriptions of the various organs, there was found a pronounced pneumonia alba, osteochondritis syphilitica, interstitial hepatitis, as well as miliary gummas in the liver, and a subacute glomerulonephritis. The thymus was of normal size, but quite fibrous. The cysts to be described later were not seen in the single cut made through the organ.

Pathologic Histology.—After fixation in Orth's fluid, sections were made from various regions from paraffin blocks and stained with hematoxylin and eosin, Van Gieson's, Mallory's and Giemsa's method. Levaditi's method for spirochetes was tried, but proved unsuccessful in all organs, due most likely to the unsuitable fixation.

When one examines the sections one is at once struck by the great number of Hassall bodies scattered not only throughout the medulla, but also in the cortex of the gland. The word "cortex," in fact, can hardly be used, as the reticular epithelium is in such preponderance over the small thymic lymphocytes that there is no sharp boundary as in the normal organ. Moreover, the perilobular connective tissue shows a marked fibrous increase, and throughout the parenchyma of the gland itself are broad areas which are almost entirely fibrous and even hyaline (Fig. 1).

In the upper part of the thymus are situated the cysts. The largest is about 3 mm. in diameter. Another is somewhat smaller, and two others consist of narrow slits about 0.5 to 1 mm. in breadth. The cysts are lined with a layer of epithelial cells which resemble somewhat in appearance the stratified squamous epithelium of the pharynx. In some places this layer shows local thickenings, and in these Hassall bodies are seen (Fig. 2). The larger cysts occupy almost an entire lobule of the gland and contain a granular detritus in which are a few lymphocytes and polymorphonuclear cells. The perilobular connective tissue is considerably thickened and forms a dense fibrous capsule around the cyst and its epithelial lining.

The local thickenings of the epithelium and their enclosed Hassall bodies furnish evidence as to the true nature of the epithelial lining. This is evidently simply the hypertrophied epithelial reticulum of the thymus, which by crowding together of its cells, along with the disappearance of the thymic lymphocytes, ultimately forms an almost solid layer of cells. The cyst, which is constantly increasing in size by a process to be described later, encroaches more and more on the lobule which contains it, so that in the end the thymus tissue consists merely of a thin layer of closely approximated reticular epithelial cells, with here and there a large remnant of the same cells, which may contain Hassall bodies, forming the local thickenings above described (Fig. 2).

The hypertrophy of the reticular epithelium which plays such an important part in this process is not limited to the neighborhood of the cysts, however. In every part of the organ the same appearance is seen. The lymphocytes are scarce, even entirely absent in some regions, and the tissue is composed of cells with a large amount of clear, light-staining protoplasm and a large, oval, vesicular nucleus. Their resemblance to the "epithelioid cells" of the granulomas is marked, and they have been given this name by many writers. Figure 3 shows the epithelial nature of the thymus tissue in the neighborhood of a Hassall body. The lymphocytes are almost entirely absent, in comparison with the large number seen in the normal gland.

Closely related to this hypertrophy of the reticular epithelium is the large number of Hassall bodies. These, as before stated, are not limited to the medulla of the gland, but are found scattered irregularly throughout the lobules, some lying at the very periphery. The large number is evidently constantly increasing, as on close examination the new development of these structures is easily studied. The manner of formation is identical with that described by Hammar[9] for their normal development. "The formation seems to begin by a cell of the reticulum—more rarely a pair of cells—increasing notably in size and assuming a spherical shape; when they reach the neighboring cells by this growth, these are compressed by the pressure produced by the growing cells and wrap themselves in layers around the central cells. Also, the peripheral cells soon become hypertrophied, by which process the formation grows and new cells are added to its periphery." These words of Hammar could not be improved on to describe the excessive development of Hassall bodies in this abnormal thymus.

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[9] Hammar, cited from Wiesel, J.: Pathologie des Thymus, Ergebn. d. allg. Path. u. path. Anat., 1911, **15**, Part 2, p. 474.

A similar exaggeration of the normal changes of the Hassall bodies is seen in their further development. Just as the normal Hassall bodies degenerate, so the new ones rapidly undergo regressive changes, and here, as in their excessive development, the process proceeds more rapidly and beyond the limits seen in the normal. Almost as soon as the clumps of the hypertrophied reticular cells can be recognized as Hassall bodies, the central cells show necrotic changes. By the time the structure has reached the average size seen in the normal thymus, it consists of a single layer of flattened epithelium with a necrotic, granular center. But while in the normal degeneration of these bodies the process comes to a standstill at this point, in this case it continues, the surrounding reticular cells forming a new layer around the degenerating center. The Hassall body, which may now be termed a small cyst, increases in size, but its structure remains quite similar to that seen in the earlier stages of the process. Figure 3 shows such a cystic Hassall body with its thin lining of epithelial cells. It is about three times the size of the larger Hassall bodies seen in the normal thymus.

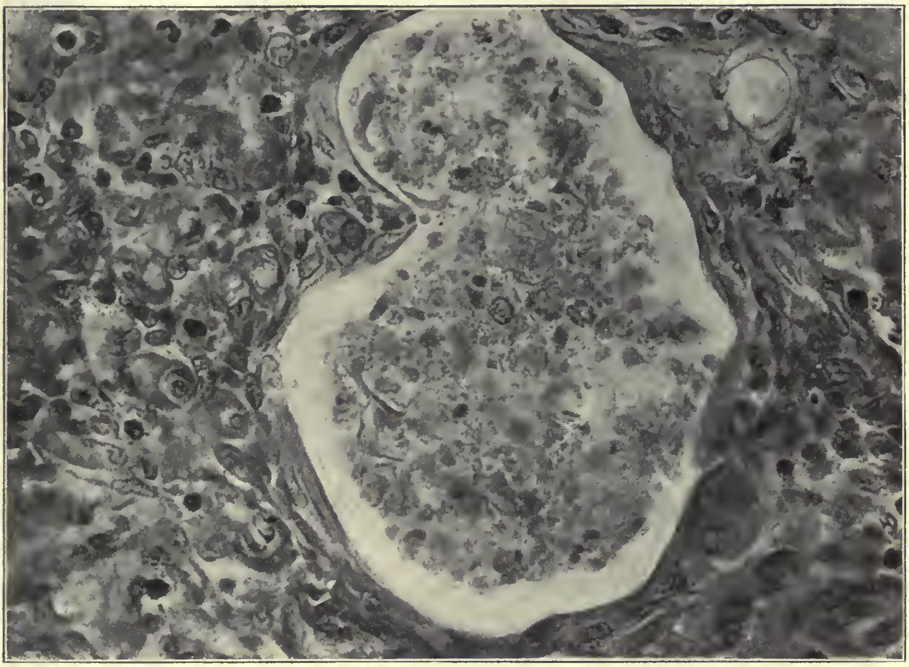

Fig. 3.—A dilated Hassall body about three times normal size. The character of the detritus and the epithelial lining of the structure are shown. Around the body the tissue is almost entirely epithelial, with a few lymphocytes. B. & L. Oc. 1. Obj. 1/6 in.

How far this cystic dilatation of the Hassall bodies might go is impossible to say, as another factor now comes into play. As has already been mentioned, the number of Hassall bodies is greatly increased, so that they lie quite close together. When they reach a certain size in their dilatation, they come in contact with each other and then fuse by rupture of the thin epithelial wall which separates them; Figure 4 shows the process very clearly. A long sinuous cavity has been formed by the coalescence of the dilated Hassall bodies, while at the extremities of this cyst the process is still incomplete. If the process had gone on to completion, one sees that the lobule would have been entirely converted into a cyst similar to the large one heretofore described (Fig. 1), with the bordering remnants of the hypertrophied reticular epithelium forming the lining of the cavity. The clump of dilated Hassall bodies at the upper right hand corner of Figure 4 might furnish a local thickening of this lining, similar to that seen in Figure 1.

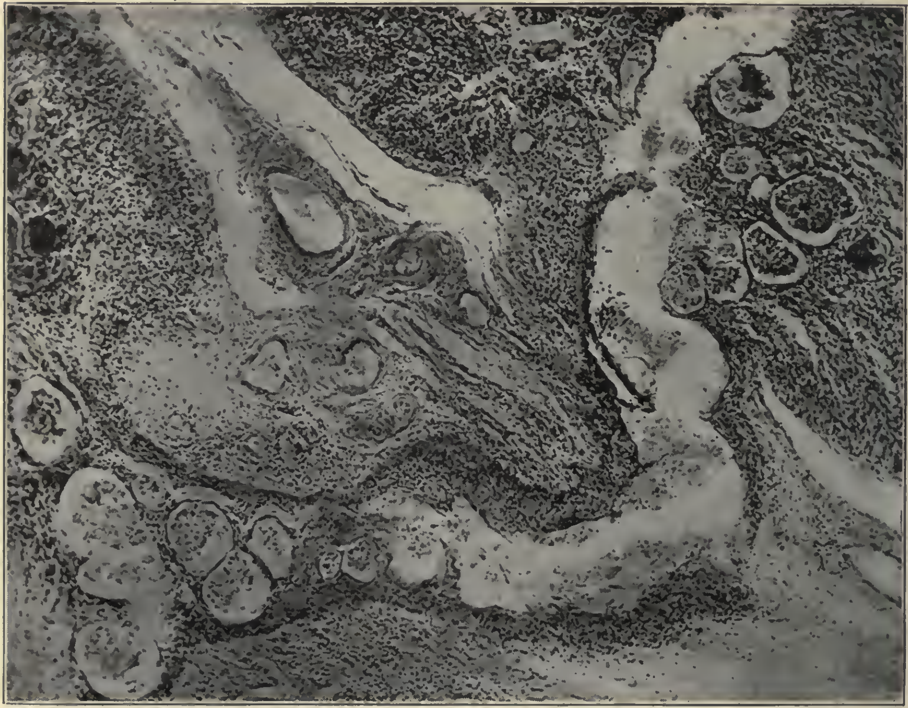

Fig. 4.—A narrow lobule of thymus tissue (dark) stretches across the lower part of the figure and connects two larger masses on each side. The lighter staining perilobular connective tissue is greatly thickened and shows an infiltration with round cells. The central part of the lobule has been transformed into a cavity, and at both extremities of this cavity the process can still be seen in progress, the dilated Hassall bodies fusing with each other. B. & L. Oc. 1. Obj. ⅔ in.

Before concluding the description of the pathologic findings, a word on the appearance of eosinophilic cells may be said. A large number of these were found scattered indiscriminately throughout the gland. There seemed to be no relation in their distribution to the degeneration of the Hassall bodies. These cells could be divided into two groups on the basis of their morphology. One type was the typical eosinophilic polymorphonuclear leukocyte of the circulating blood and that seen in the tissues in certain pathologic conditions. An equal number, however, were larger cells, with a large oval nucleus rich in deeply staining chromatin, and with a large, irregular protoplasmic body filled with densely packed eosinophilic granules. These granules stained a more purplish-red than those of the typical eosinophilic polymorphonuclears. It seems probable that these are reticular epithelial cells, and that the granules represent phagocytosed granular material. It is interesting to note that the necrotic material of the Hassall bodies stains a similar color with Giemsa.

To sum up the pathologic findings of the case, we may say that we have to do with a thymus from a congenitally syphilitic infant in which cysts were present. These cysts had arisen by the cystic dilatation and coalescence of the Hassall bodies. Along with this degeneration of the Hassall bodies was an equally important hypertrophy of the reticular epithelium and new formation of concentric corpuscles, for without these progressive changes, it is doubtful if the cystic cavities could have arisen.

Which of the two processes is primary is difficult to say. One is apt to think in a general way of degeneration as the primary, with a compensatory hypertrophy. The presence of spirochetes (which unfortunately could not be demonstrated for technical reasons) might explain the rapid and early degeneration of lymphocytes and Hassall bodies, with a resulting release of "pressure" on the epithelium of the reticulum, and a hyperregeneration of the destroyed structures. The areas of fibrosis might also be explained in like manner. Whatever the relationship between the two processes, we can surely say that the cystic cavities in this case are not due to the developmental arrest, and have no connection with the original central cavity of the embryonic thymus. They have arisen from the cystic Hassall bodies in much the way described by Chiari and Schlesinger. As pointed out by Pappenheimer in his case, the large areas of fibrosis also show more than a developmental lack of differentiation.

How, then, are we to explain those cases in which a different origin of the cysts has been described? It would seem that in many of these the process had gone on to such a degree that the origin, which might well have been by the method here described, had been obscured. This would also explain the absence of Hassall bodies in these cases, as these structures tend to disappear with the increase in size and number of the cysts.

Another point demonstrated by this early case is the unity of the syphilitic processes in the thymus. Both Simmonds and Pappenheimer describe two types of lesions in such organs: one, the more rare, in which cysts are present, and those in which there is an epithelial hyperplasia with disappearance of the lymphocytes. Both types of lesion are found in the present case, and the former seems definitely dependent on the hyperregeneration of the degenerating Hassall bodies which goes hand in hand with the hypertrophy of the reticulum, for without a large number of these structures, fusion and the formation of large cysts would be impossible.

CONCLUSIONS

Syphilitic disease of the thymus in infants is manifested primarily by a degeneration of the lymphocytes and Hassall bodies, with a hypertrophy of the reticular epithelium and hyperregeneration of the concentric corpuscles. The process may give rise to the formation of cystic cavities by the dilatation and fusion of the degenerating Hassall bodies.

I wish to thank Dr. Ophüls for his kindness in reviewing this study.

CLINICAL DEPARTMENT

CONGENITAL ATRESIA OF THE RIGHT AURICULO-VENTRICULAR ORIFICE WITH COMPLETE ABSENCE OF TRICUSPID VALVES *

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Congenital atresia of the tricuspid orifice is a rare condition and to make this anomaly compatible with life, it becomes necessary that there be patent foramen ovale or at least an opening in the interauricular septum and that the two ventricles communicate. Associated with these, there may also be a patent ductus arteriosus. When the conditions mentioned above are the only anomalies, such a case is spoken of in the literature as an uncomplicated case. Of such we have been able to find records of eight cases to date. As complicated cases may be considered those in which there are further anomalies, such as transposition of vessels. The case which we have had under observation is as follows:

E. L., 8½ months old, was admitted to Michael Reese Hospital Nov. 5, 1914, and died Nov. 12, 1914, after having been under our observation for about four months.

The child had been ailing from birth, with marked difficulty in breathing and occasionally attacks of cyanosis. Five weeks before death the child had a much aggravated attack of dyspnea and very marked cyanosis, lips and face being very blue, the attack being accompanied by acute intestinal symptoms. This attack passed away and two weeks later the child awoke during the night, crying, as if in great agony; the eyes began to bulge, and he became very restless, his respirations being very short, labored, and superficial in character. The child became markedly cyanotic, the pulse being rapid and very weak and for several hours the mother feared that the child would die. The onset of this attack was sudden, without any fever, convulsions or vomiting. The attack passed off and during several days immediately before admission to the hospital the child had many other similar attacks. There was much loss of weight after the attacks became marked, but no fever throughout. The child suffered with bilateral otitis media, both ears discharging after the attack of pneumonia at 2 months of age. During the summer the child had several attacks of diarrhea, each of which lasted from seven to ten days.

The child was born at full term, the delivery being entirely normal without any attacks of asphyxia. The baby weighed 7½ pounds at birth. He was breast fed exclusively for about two months and artificially for the rest of his life.

The family history was negative, except that the mother had one miscarriage two years before, which, however, was due to an accident.

On admission the child weighed 8 pounds 3 ounces, the temperature was 95.6 F., pulse 112 and respirations 40 per minute.

The general appearance of the patient was that of an underdeveloped infant, with markedly protruding eyes, very marked cyanosis, rapid, irregular, labored breathing, rapid, irregular pulse, clubbed fingers and toes. The anterior fontanel was soft, large and slightly retracted. The posterior fontanel was closed. The suture lines about the occiput were palpable. The occiput was very prominent. The veins over the entire head were prominent and the pulse at times was very distinct about the head. The skin showed a marked sclerema and was of almost board-like consistency. The eyes were cyanotic, and there was marked exophthalmos, the pupils being equal in size and moderately dilated and reacting to light. Both ears were discharging a large quantity of very foul, thick, greenish-yellow pus. There was no apparent mastoid tenderness. The throat was negative. The lips were cyanotic, dry and covered with small scales, and the tongue was coated. No teeth had erupted. The neck was retracted and very rigid. All the vessels in the neck were greatly filled and pulsated. The venous pulsation was very marked. A marked in-drawing was seen in the suprasternal notch. The liver was palpable almost at the level of the umbilicus, having a hard, rounded edge. The spleen and kidneys were not palpable. The genitals showed slight cyanosis, no discharge. The extremities were markedly cold and cyanotic, the tips of fingers and ends of the toes clubbed and especially cyanotic. There was no marked tenderness and no other deformity. There was some rigidity of the spine, with marked retraction of the head, but otherwise the spine was negative. There was a slight Brudzinski, a suggestion of Kernig, no Babinski, no tache cerebrale and no clonus. The patellar reflexes were exaggerated.

The intercostal spaces were somewhat retracted and the veins over chest were dilated. The lung findings were negative. In the fifth interspace a diffuse apex beat could be seen. On percussion the boundary of the heart on the left side was found to be just at the nipple line, on the right side about 0.5 cm. externally from the right sternal border. The upper border was at the second rib. Over the base a long, loud systolic murmur was heard, which was thought to be best heard over the pulmonary region. No murmurs were heard at the apex.

Blood examination on the day of admission showed 85 per cent. hemoglobin, 4,500,000 erythrocytes, 12,700 leukocytes, the differential being 20 per cent. polymorphonuclear neutrophils, 60 per cent. small mononuclears, 13 per cent. large mononuclears and 7 per cent. transitionals.

From the foregoing findings a diagnosis was made of congenital heart disease, passive congestion of the liver and bilateral otitis media.

On the day of admission the child's temperature was subnormal (95.6 F.) and after that the temperature curve was irregular, rising in the first three days to 101.8 F. at 8 p. m. on the third day, then suddenly dropping to subnormal, 95.2 F., at midnight of the same day; then being slightly above the normal, it rises to 102.6 F. in the morning of the day of death, but falling to 97.5 F. shortly before death. Pulse-temperature and pulse-respiration ratios were not disturbed.

On the first day the child took nourishment poorly, retaining only about one half. It was losing weight continually, the last weighing before death showing 7 pounds 4 ounces as compared to 8 pounds 3 ounces on the day of admission. Especially during the attack of dyspnea and cyanosis the food was taken very poorly or sometimes not at all. On the day of death the child suffered with marked cyanosis, respirations being very labored, and it was unable to take any food. The ears continued to discharge pus. The child died eight days after admission to the hospital.

A roentgenogram of the heart (Fig. 1) shows a very broad shadow at the base, with a marked bulging in the region of the right auricle. A similar broadening is also seen in the region of the left auricle. The transverse diameter of the shadow is also much greater than would be expected in an infant of this age. This broadening of the shadow involves both the right and the left sides of the heart. Compared with the necropsy findings, the broad basilar shadow was seen to be due to enlarged right and left auricles, and the broad transverse diameter of the lower part of the shadow in part to the large left auricle and in greater part to the large left ventricle.

At necropsy the organs were found to be normal, with the exception of mottling and congestion of the liver and marked abnormalities in the heart. The heart extended from the second to the seventh intercostal space. Practically the whole base of the heart was composed of the right auricle, the right ventricle being a small cavity which appeared almost as an appendage to the right auricle, and was located at the base of the heart about the level of the auriculoventricular septum, with its greatest diameter placed transversely and its cavity about the size of a large lima bean. The body of the heart was composed of the left ventricle, which was greatly hypertrophied. The left auricle was also greatly enlarged. The right auricle was prominent, immensely dilated and of a dark blue color. The foramen ovale was large and open. The tricuspid orifice and tricuspid valve were absent, there being nothing to mark the place where they should be. The interventricular septum was perforated by a small opening located at the upper part of the left ventricle, and this opening was about one sixteenth of an inch in diameter. The mitral orifice was dilated, being of such a size that a finger could be passed through easily and the mitral valve was very large, the papillary muscles being of exceptional size, and being attached obliquely rather than transversely as normally seen. The ductus arteriosus was rather small but patent. The aorta and pulmonary arteries were in practically normal relation, as were also the pulmonary veins

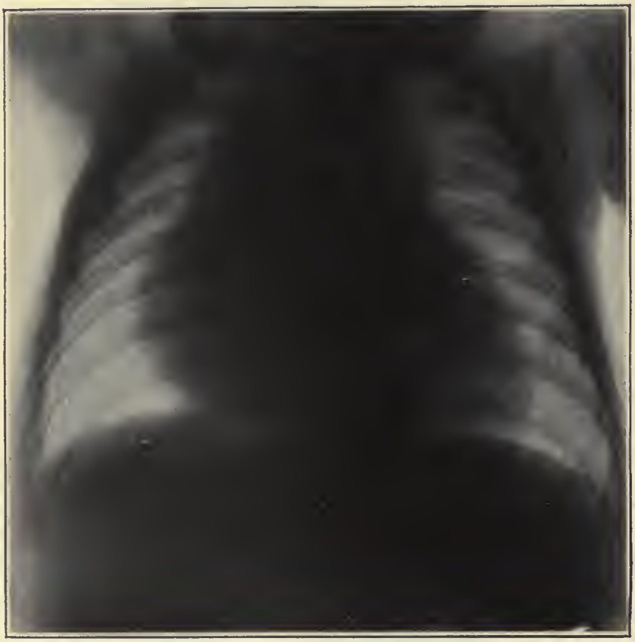

Fig. 1.—Outline of heart, with broad shadow at the base and marked bulging in the region of the right auricle.

and vena cava, except as they were displaced at their origin due to the malposition of the various orifices of the heart. The pulmonary artery showed no stenosis, although as a whole it was considerably less in caliber than one would find in a normal heart. The pulmonary arteries were normal in structure although of smaller size than normal.

According to these findings the blood current in the heart was as follows: All venous blood went from the right auricle into the left auricle, thence to left ventricle, thence most of it went into the aorta and systemic arteries. A small percentage (possibly about 20 per cent.) went through the interventricular foramen into the right ventricle and thence into the pulmonary artery and lungs, and a very small percentage of this was shunted by the dulcus arteriosus into the aorta.

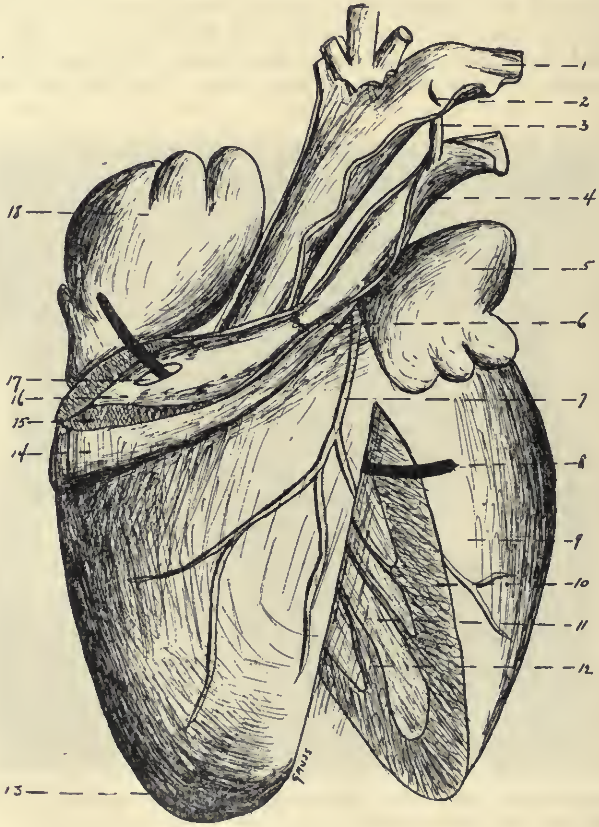

Fig. 2.—Anterior view of the heart, dissected: 1, aorta; 2, orifice of ductus arteriosus; 3, patent ductus arteriosus; 4, pulmonry artery; 5, left auricle; 6, pulmonary valves; 7, anterior coronary artery; 8, probe in interventricular opening; 9, left ventricle; 10, left wall; 11, left ventricular cavity; 12, papillary muscle to mitral valve; 13, apex of heart; 14, right ventricle; 15, right ventricular wall; 16, right ventricular cavity; 17, interventricular opening; 18, right auricle.

Summing up the case, we find that the chief abnormality was the tricuspid atresia, which, not admitting blood to the right ventricle, resulted in arrested development. The atresia was partly compensated by an open foramen ovale, which, however, was not entirely sufficient and thus general venous congestion was produced. As less than one fourth of the blood reached the lungs by way of the abnormal interventricular opening, the blood was not sufficiently aerated, was abnormally rich in carbon dioxid and produced cyanosis. Thus the tricuspid atresia seems to have been the primary lesion, all the other abnormalities being somewhat of a compensatory character.

On the symptoms of attacks of cyanosis and dyspnea, clubbing of fingers and toes, venous congestion, enlargements of the heart and wide mediastinal shadow as seen by the roentgenogram (Fig. 1), and systolic murmur at the base, a diagnosis of congenital heart disease was made, the nature of the abnormality and full extent of the lesions remaining problematic until the necropsy was performed.

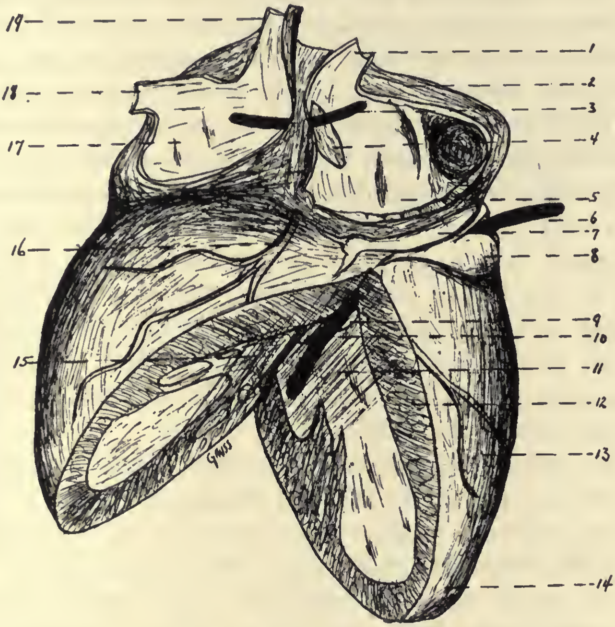

Fig. 3.—Posterior view of the heart, dissected: 1, superior vena cava; 2, right auricle; 3, probe in patent foramen ovale; 4, patent foramen ovale; 5, dependent portion of right auricle, showing no evidence of tricuspid valves; 6, probe in interventricular opening; 7, coronary sinus; 8, right ventricle; 9, interventricular opening; 10, entrance to aortic orifice; 11, left ventricular cavity; 12, left ventricular wall; 13, left ventricle; 14, apex of heart; 15, mitral valve; 16, posterior coronary artery; 17, left auricle; 18, pulmonary veins.

Congenital tricuspid atresia (aplasia ostii venosi dextri) is one of the rarest congenital anomalies of the heart. Rauchfuss[1] in his work on the diseases of the circulatory organs in children gives only five cases as found by him in the literature. The cases were those described by Kreysig, Vrolik, Nuhn, Valleix and Peacock. Vierordt[2] in 1901 adds to these five cases three more, those of Chapotot,[3] Gelpke[4] and Aschoff-Schreiber.[5] Kühne[6] describes two further cases of her own of tricuspid atresia. Wieland[7] describes one case of his own, which makes eleven cases in all.

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[1] Rauchfuss: Die Krankheiten der Kreislauforgane, Gerhardt's Handbuch d. Kinderkrankheiten, 1878, **4**.

[2] Vierordt: Die angeborenen Herzkrankheiten, Nothnagel's spez. Path. u. Therap., Vienna, 1901, **15**.

In all the cases described there had been present, besides the tricuspid atresia, a defect of the septum and open foramen ovale. The ductus arteriosus was in some cases open, in others closed. In the cases of Kreysig,[8] Peacock and Gelpke there was found, besides atresia of the tricuspid, a transposition of the large vessels; in Klug's case a growing together of the two pulmonary valves, also narrowing of the pulmonary artery, otherwise described as normally large.

It is evident that one must separate complicated cases of heart anomalies from uncomplicated, simple and typical tricuspid atresia, as shown by Kühne in her work. As a simple tricuspid atresia may be regarded those cases in which there are septal defects and open foramen ovale, these being regarded as necessary accompaniments of the tricuspid atresia. While it is possible that they are direct adjustments to the tricuspid atresia, yet they are conditions which are absolutely necessary for the life of the individual. The cases of Kreysig, Peacock, Gelpke and Klug were complicated by other anomalies, which leaves seven uncomplicated cases, to which Wieland adds also Sieveking's[9] case as uncomplicated tricuspid atresia, thus making eight cases, our own case making the ninth.

In all its findings our case resembles these simple or uncomplicated cases of tricuspid atresia, the necropsy findings being also very similar. Antemortem diagnosis in those cases was also only congenital heart disease, the necropsy later showing the exact abnormalities.

As to the age at which the patients in these so-called cases of isolated tricuspid atresia died, according to Kühne all died during the first year of life, with one exception, Chapotot's girl, who reached the age of nearly 2 years. Our patient also died in the first year of life at the age of 8½ months. Other patients with tricuspid atresia, complicated with other heart anomalies, lived longer: Vrolik's patient nine years, Favell's[10] ten years, Holmes'[11] twenty-one years, Gelpke's twenty-seven years, and in the last case published by the Basel Pathological Institute the patient lived fifty-three years.

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[3] Chapotot: Lyon méd., 1889, **62,** 424.

[4] Gelpke: Seltener Fall von angeborenem Herzfehler, Inauguraldissertation, Basel, 1883.

[5] Aschoff-Schreiber: Deutsch. med. Wchnschr., 1901, Association Supplement, p. 63.

[6] Kühne, M.: Ueber zwei Fälle kongenitaler Atresie des Ostium venosum dextrum, Jahrb. f. Kinderh., 1906.

[7] Wieland: Zur Klinik und Morphologie der angeborenen Tricuspidalatresia, Jahrb. f. Kinderh., 1914, **79,** 320.

[8] Kreysig: Krankheiten des Herzens, Berlin, 1817, **3,** 104.

[9] Sieveking: Tr. Pathol. Soc., 1854, **5,** 97.

The course and clinical symptomatology of congenital tricuspid atresia are those of a congenital pulmonary stenosis, with the distinction that in the formed one there is a hypertrophy of the left ventricle, while in the latter, a hypertrophy of the right ventricle. Furthermore, the systolic murmur heard in all cases is said to be more pronounced to the right of the sternum in tricuspid atresia, and to the left of the sternum in pulmonary stenosis. As in pulmonary stenosis, the children are affected by cyanosis and dyspnea. The heart pulsations are spread generally over the precordium.

Important in the diagnosis of tricuspid atresia is the hearing of loud systolic murmur, having its point of maximum intensity at the base of the heart (sternum), the intensity diminishing from that part. In pulmonary stenosis the murmur is loudest and heard best in the second left intercostal space. Murmurs in congenital anomalies of the heart are known for their constancy.

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[10] Favell: Province méd., **3**, 440.

[11] Holmes: Edinburgh Med. and Chir. Tr., 1824, **1**, 252.

PROGRESS IN PEDIATRICS

RECENT WORK IN ANATOMY, PHYSIOLOGY AND PATHOLOGY OF CHILDHOOD *

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ANATOMY

THE PARATHYROIDS

The relative position and histologic anatomy of the parathyroid glands, from early fetal life up to advanced age, have recently been studied by Thimm.[1] His material was quite varied: neck organs from over a hundred bodies, mostly adult; material from the eleventh and fifteenth year; some infants under 2 years of age (three prematurely born infants, sixth and seventh month); serial sections of three embryos of 3 cm. length, 5 weeks and 2½ months, respectively, and, finally, a variety of lower animals, laboratory animals, and others from zoological gardens. The work was done under the supervision of Professor Hansemann.

Thimm found the anatomic position of the superior pair of parathyroid bodies very constant. The inferior pair, on the contrary, are often pushed laterally, seldom up or down, by swelling of neighboring lymph glands, tumor formation, and the like.

In size the bodies measure 2 to 4 mm., in 1- to 2-year-old children, and are not yet flattened, oval or leaflike, as in the adult, but more globular in shape. In adults they are ellipsoid, leaflike, or very flat, and measure about 3 by 5 by 6 to 10 mm. Where they are as much as 12 mm. long, they are unusually narrow, for example, 12 by 3 mm.

The color of the parathyroid bodies varies considerably in microscopic preparations (Halsted technic). Characteristically, the parathyroid bodies take a reddish tone. Most commonly they take a lighter shade, one between this and yellow. In cachectic and anemic individuals the color becomes entirely yellow, and the whole parathyroid body closely resembles fat. Usually, however, the gland can be distinguished from fat in the neighborhood by the somewhat lighter color of the latter.

When a distinction can be made between the individual glands, the

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* Submitted for publication Dec. 10, 1916.

[1] Thimm, L.: Zur Kenntniss der Epithelkörper (Glandulae Parathyroidae), Arch. f. Kinderh., 1914, **63,** 321.

lower pair usually correspond in size. The upper pair tend to be smaller and more yellow, like adipose tissue. The lower stand out in sharper contrast with the surrounding tissue, and, when not in direct contact with the thymus gland, present a more typically elongated or oval form.

Thimm is impressed with the fact that the parathyroid bodies are found well preserved and strikingly constant and symmetrical in position, even in advanced age.

He found no true accessory thyroid glands (in human material). Projecting portions of the main glandular mass may be so cut as to present in sections the appearance of isolated bodies, but further study of the sections invariably showed that these were but part of a single glandular mass. Thimm did not find more than two parathyroid bodies on any one side, nor more than four in all. He is not familiar with the histologic picture of the "carotid glands."

The curvature of the neck region in embryonic life is associated with a certain amount of overriding of the branchial arches and clefts. This has some influence on the relative positions of the derivatives of the structures.

In the 3.5 cm. human embryo, Thimm found the two superior parathyroid bodies present in two fully symmetrical, clear-staining, round bodies lying on the posterior surface of the lateral margins of the developing thyroid. Immediately below each of these and somewhat laterally and ventrally, lay a larger, less globular, but otherwise entirely similar body, of like cell type, the inferior parathyroid of that side. Each of these bodies was continued distally, as a cell column with a more or less well-defined lumen which passed over medially into the thymus, the nuclei assuming the form characteristic of the thymus. These cell columns Thimm regards as the last remains of the cleft groove, the third medial branchial cleft, from a dorsal thickening of the wall of which arises the parathyroid, and from a ventral thickening, the thymus.

The relative position of the superior and inferior parathyroid bodies in the adult is already indicated in the 3.5 cm. embryo, the latter lying ventral and laterally to the former, though here still in actual contact with it. Through the relations of the lower mass to the thymus, the inferior parathyroid bodies are drawn downward as the thymus follows the heart in its descent and are pushed laterally as the thymus enlarges.

In the 5-weeks-old human embryo, the superior parathyroid bodies were found at the level of the thyroid isthmus, or slightly above it. The inferior pair lay below and somewhat ventrally to them and immediately adjacent to the thymus tissue. No distinct connection between the thymus and adjacent parathyroids could be demonstrated in this instance. In the 2½ months fetus, only one parathyroid body was found on the left side, and it occupied an intermediate position. It could not be determined whether this represented the superior or the inferior parathyroid body.

According to Thimm, the vascular system can often be clearly distinguished in serial sections of uninjected tissues. He pictures the vascularization of the parathyroid bodies as follows: An arterial stem enters at the hilus and divides into a number of branches of equal size. These subdivide into smaller vessels, and eventually into a network of capillaries. Adjacent to these lie lymph spaces bathed with tissue juices. The veins arising from the capillary network proceed directly to definite centers, or to the hilus. Broad lymph spaces accompany them to the hilus, or, in peripheral regions, proceed to the capsular spaces and thence to the hilus. Any secretion probably occurs into the lymph spaces.

As regards the types of cells found in the parathyroid bodies, Thimm recognizes the four types described by Welch.[2] He finds, however, that the oxyphilic cells appear first after the twentieth year of life, and increase in number with age. They never at any time form a considerable proportion of the cells.

No undoubted secretory globules (*Tröpfchen*) were found in material from children under 2 years of age, nor, though the examination here was not so extensive, were any found in material from a boy 15 years of age. The tissues were stained with hematoxylin and eosin.

Staining tissues with sudan III revealed small and very fine fat droplets scattered over the entire section. Occasionally evidences of past hemorrhages (Erdheim) were found, and in one instance (tissues from an individual who died of chronic lead poisoning at an advanced age) there were found, in the oxyphilic cells, minute round golden droplets with a surrounding clear zone; these were thought to be altered blood pigment, and were present also in adjacent connective tissue.

THE TONSILS

Though possession of exact knowledge of the relation of the tonsils to the adjacent structures would seem to be a matter of some importance in operative procedures on them, G. Hudson Mackuen[3] has recently called attention to the common lack of knowledge regarding the nature of the so-called "capsule" of the faucial tonsils, and its relation to the intrapharyngeal fascia.

If the faucial tonsils possess a true capsule, removal of the tonsillar tissue and the subjacent capsule would seem to be the cleaner surgical procedure, and one that would prevent further growth of adenoid tissue in this location. If, however, the connective tissue lying immediately subjacent to the adenoid (tonsillar) tissue and closely attached to it is but part of the intrapharyngeal fascia, or aponeurosis, that encircles the pharynx, then to remove that portion of it which lies just behind the tonsil may be but to form a window in the sleeve of fascia that underlies the mucous membrane of the pharynx, and interposes a barrier between this and the loose connective tissues of the neck and mediastinum. Such a window or defect might be conceived of as permitting ready entrance into the body of bacteria and the products of inflammation.

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[2] Welch: Jour. Anat. and Physiol., 1898, **32,** 292.

[3] Mackuen, G. Hudson: The Surgical Anatomy of the So-Called Capsule of the Faucial Tonsil, Laryngoscope, 1915, **25,** 685.

Mackuen quotes Dr. D. R. Patterson, special throat surgeon to the King Edward Hospital, Cardiff, as one who has made careful study of the anatomy of the faucial region, both in man and the lower animals. Patterson says the so-called capsule of the tonsil is merely a portion of the intrapharyngeal fascia or aponeurosis, having its upper attachment at the base of the skull and extending down into the region of the esophagus. In confirmation of this belief he quotes freely from the English and French schools of anatomy. This view Mackuen endorses on clinical grounds.

Adenoid tissue is found everywhere in the mucous membrane that clothes the fascial layer surrounding the pharynx. At the side of the future faucial tonsils this adenoid tissue undergoes a relatively great development, or hypertrophy. That in the vault of the pharynx undergoes a lesser development; when excessive or obstructive it is spoken of as an adenoid growth or vegetation. Mackuen says:

> In the course of its development in the embryo and during infancy, the tonsil appears to appropriate a portion of the connective tissue and musculofibrous tissue with which it is in juxtaposition, and finally, in adult life, it becomes firmly attached to the membrane, to which has been given the name intrapharyngeal aponeurosis, and a section of which seems to constitute the so-called capsule of the tonsil.

The closeness of the union increases with age, and is the result of physiologic as well as pathologic processes. The blood supply of the tonsil, passing through the intrapharyngeal aponeurosis, tends to bring about a still firmer union between the tonsil and its capsule. In very young children, the mass of adenoid tissue (tonsil) may at times be peeled out of its bed or pocket with very little connective tissue attached to its surface. This may be so scanty and so delicate as to suggest that it is merely a compressed portion of the subareolar connective tissue in which the adenoid (tonsillar) tissue happens to be embedded. With increasing age, closer and closer union takes place between the tonsil and the aponeurotic fascia. The tonsil seems to grow fast to the membrane, and more and more of it is torn away in attempts at removal. The occurrence of pathologic processes favors this closer union.

PHYSIOLOGY

BODILY DEVELOPMENT

T. I. Grover[4] finds that the head and breast measurements of a child stand in closer relation to weight than to age; that the length of the arms and legs is in direct relation to the height; and that, in general, one can judge of a child's development better by his weight and growth than by his age.

Max Guttmann[5] gives statistics from individuals measured on the day of birth and thereafter, with great exactness, through a series of years, even up to the age of 28. The details are too numerous for abstracting.

ELECTRICAL REACTIONS OF NORMAL CHILDREN

That it is possible to detect certain states of abnormal excitability of the nervous system by the determination of what is called the electrical excitability of a typical peripheral nerve has been held by pediatrists for many years. The degree of electrical excitability is expressed in terms of the number of milliamperes of galvanic current required to provoke minimal contractions in the muscles supplied by, for example, the ulnar or the peroneal (external popliteal) nerve. In typical instances of hyperexcitability, contractions may be obtained in each phase of galvanic stimulation; that is, there is a contraction of the muscles with making and with breaking both the cathodal and the anodal (or reversed) current. In most normal individuals, however, the muscles contract in only two or more of the four phases, unless excessively strong currents are employed. The amounts of currents required in each instance to produce minimal contractions are called the "electrical values" of the individual.

The most characteristic form of electrical hyperexcitability of the nerves is seen in the condition known as tetany. Erb called attention to the presence of this increased electrical excitability in adult patients suffering from tetany, and later workers showed that it is found also in cases of the disease in infants and children. At the same time Erb advanced the hypothesis that there occurs a latent form of the disease in which the other characteristic phenomena or symptoms of tetany may be in abeyance and a diagnosis of the presence of disease possible only through a demonstration of abnormal electrical values.

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[4] Grover, T. I.: Some Measurements of Normal Children, Arch. Pediat., 1915, **32,** 472.

[5] Guttmann, Max: Einige Beispiele individueller körperlicher Entwicklung, Ztschr. f. Kinderh., 1915, **13,** 248.

Stintzing, in 1886, examined a large number of persons of various ages with the faradic current and published tables giving the mean value for each of the peripheral nerves and the normal range of variation therefrom that may be expected. These Stintzing tables are made the basis of clinical neurologic investigation, being accepted as the standard of normality. Stintzing recorded also the cathodal closing values, but he did not investigate the values for the other phases of galvanic electrical stimulation. It is the determination of these other values that has proved most serviceable in the study of tetany.

Escherich, Thiemich and Mann, and finally von Pirquet, studied the galvanic electrical reactions as they occur in infants and very young children. The standards established by these authors for infants and young children have been utilized by other workers for older children, even those approaching puberty. It has been assumed that the standards for electrical reaction in infancy were applicable, without modification, to children of 5, 10, or more years of age, and not a little confusion has resulted.

It has become evident that the galvanic electrical standards of infancy are not applicable without modification to older children; and that there is a change in the normal galvanic electrical values that is more or less coincident with change in age.

Holmes[6] has recently examined the galvanic electrical values in a large number of children in each year of life from birth to puberty. The results of his study have been summarized as follows:

1. There is a gradual transition from the high electrical values of early infancy to the relatively low values of adult life.
2. Values below 3 milliampères, other than cathodal closing values, are rare in the first six months of life, but appear with increasing frequency thereafter.
3. Cathodal opening contractions with a current of less strength than 5 milliampères are of infrequent appearance in normal children of any age; they probably do not occur in normal children under 5 years of age. The same may be said of cathodal closing tetanus.
4. The presence of anodal opening contractions with a current less than that causing anodal closing contractions and under 5 milliampères (anodal hyperexcitability), occurs with gradually increasing frequency from the first half year of life upward, reaching its maximum frequency in children of 6 or 7 years.

The actual figures obtained are given by Holmes in two tables. The first table gives the *average* values found in normal children in each year of life. Not all children present the average or mean value. Stintzing showed that in adults quite a wide range of normal variation might be expected; for example, the cathodal closing value may be 0.2 to 2.0 milliamperes for the peroneal nerve at Erb's point, the average being 1.0 milliampere. A similar range of normal variation is found in infants and children. The extremes found in examining the same apparently normal children are given in the second table.

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[6] Holmes, J. B.: The Reliability of the Electrical Diagnosis of Tetany, etc., Am. Jour. Dis. Child., 1916, **12,** 1.

Taken together the two tables afford a standard or norm for use in examination of the galvanic electrical excitability of the nerves of infants and young children, and are thus comparable to the Stintzing tables for faradic excitability.

From the point of view of pure physiology it is desirable that the investigation be extended into adult life. The practical application of the tables, however, is to the study of conditions of latent and active tetany in infants and young children, and in this the tables are a much needed extension of the work of the authors before mentioned.

THE BLOOD

Kunckel[7] has studied the hemoglobin and cellular content of the blood of prematurely born, but otherwise healthy, infants during the early months of life. His material consisted of sixty premature infants, seven twins and seven "debile" infants. It is not certain that the last mentioned fourteen were prematurely born. Most of the children came under observation in the second or third week of life. The youngest received breast milk, others were given milk modifications and food adapted to their age. The average weight of those under two months of age was 1,900 gm. The average monthly gain in weight was somewhat over half the normal. The infants remained unusually free from coryza or other acute infections. The hemoglobin content of the blood was determined with the Sahli hemoglobinometer.

As a normal standard for comparison, Kunckel used the figures obtained by J. Levy (Detroit) from other children in the asylums of Berlin, stating, however, that Levy's figures may be too low for normal infants in general, owing to the social status of the material from which they were obtained. Levy's figures for the average hemoglobin content of the blood at various ages are: in the second month, 70 per cent.; in the third month, 65 per cent.; in later months, 50 to 60 per cent.

Kunckel found that the hemoglobin content of the blood was uniformly high (average 104.8) in those premature infants examined in the first two weeks of life; and that it then declined more rapidly than in normal full-term infants, and reached a lower level. The actual figures, average values, are: in the second month, 55.2 per cent.; in the third month, 46.5 per cent.; in the fourth month, 49.6 per cent.; in the fifth month, 52 per cent.

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[7] Kunckel, D.: Zur Kenntnis der Blutveränderungen bei Frühgeburten und debilen Kindern, Ztschr. f. Kinderh., Orig., 1916, **13,** 101.

These figures were further established by isolated observations on other healthy premature infants, the additional observations yielding results similar to the above.

The red cell count in contrast with the hemoglobin varied but little from the normal. The average for the first year, exclusive of the first month, was 4,085,000. Anisocytosis and poikilocytosis were often seen, but no other abnormalities.

The white cell count differed from the normal in that, instead of the usual 12,000 to 13,000 cells per cubic millimeter, the average between the second and the sixth month was 7,800. The count rose, as in other infants, on the appearance of furunculosis or other inflammatory processes. The morphology of the white cells was essentially normal.

In discussing possible etiologic factors for the striking relative anemia of the prematurely born, Kunckel mentions Hagouneng's observation that the content of the fetus in iron is twice as great during the last third of pregnancy as during the first two thirds. He adds, however, that this finding must be qualified by Philippson's observation that the size of the supply of iron varies considerably in fetuses in the same month of intra-uterine life.

Kunckel was not able to show that the weight of the premature infants in his material and their later hemoglobin percentages stood in any constant relation. He gives as one instance the case of twins, admitted on the eleventh day after birth, and showing approximately the same weight and erythrocyte count, who yet differed widely in their hemoglobin percentage (120 versus 80), and maintained this difference (85 versus 55, in the beginning of the second month, and 68 versus 45 at the end of the second month). Differences in tying off the cord, and the like, could hardly explain such findings.

Whatever the cause of the primary lack of iron hemoglobin may be, the condition appears to pass slowly over into the normal during the second half year. (Kunckel's observations on this point seem insufficient.) In no case did a severe anemia develop. Clinically, open air treatment led to a marked improvement in the hemoglobin percentage. The effect seemed to be due to the improvement in the general metabolism of the body, in which the iron metabolism shared.

LEUKOCYTOSIS OF DIGESTION

A. Graeme Mitchell[8] examined fifty bottle-fed infants for the occurrence of a leukocytosis during digestion. He made over 700 blood counts. He finds that bottle-fed babies do not constantly show a digestive leukocytosis; in fact, the majority show a smaller number of leukocytes in the superficial blood after taking food than before. This decrease becomes greatest from one to two and a half hours after feeding and then becomes less marked. When a rise does occur it appears most frequently soon after feeding and begins to decline in a half hour. There seems to be as yet no adequate explanation for the increase or decrease.

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[8] Mitchell, A. Graeme: Leukocyte Counts During Digestion in Bottle-Fed Infants, Am. Jour. Dis. Child., 1915, **9**, 358.

A careful review of the literature on the subject accompanies Mitchell's report. Most textbooks speak of a physiologic leukocytosis. Some standard works on pediatrics state that this leukocytosis is more pronounced in children. The majority of workers, however, hold that digestive leukocytosis is inconstant in both adults and babies.

NUTRITION

The exigencies of wartime in the central empires promise to furnish us with many practical studies in dietetics. One of the first of these comes from von Pirquet. He urges the use of increased amounts of sugar in wartime, because of the relative cheapness of this article of diet. He states that 50 per cent. of the total calories in the infant's diet may be given in this form and that older children may be given amounts up to 300 gm. daily. It is necessary in older children to increase the amount very gradually, else diminution of appetite, nausea or vomiting are produced. With this increased amount of sugar must be given much albumin (skim-milk, cheese, legumes, eggs, meat, etc.), otherwise there occurs no corresponding gain in weight.

In Austria, in 1915, the cost of 100 gm. of sugar, as compared with its nutritional equivalent in milk (600 gm.), was as ten to eighteen. (In this connection it may be mentioned that the per capita consumption of sugar in America is said to be much in excess of that of other nations.)

GASTRIC DIGESTION

Two studies on the gastric digestion of infants are reported by Finzio;[9] one on the occurrence of free hydrochloric acid in the gastric contents of infants, and another on the power of the gastric secretion in infancy to digest casein.

Finzio finds that the amount of free hydrochloric acid in the stomach content of infants is closely dependent on the milk diet. (In adults free hydrochloric acid may be lacking in the gastric contents after a milk meal or diet.) In adding progressively increasing quantities of a normal solution of hydrochloric acid to mixtures of mothers' milk and pepsin, he finds that digestion occurs in the presence of a deficit of "free" hydrochloric acid (0.1168 gm. HCl is bound by 100 c.c.

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[9] Finzio, G.: Valore dell' acido cloridrico libero nel contenuto gastrico del lattante, La Pediatra, 1915, **23,** 168.

of mothers' milk), but that it increases gradually as the deficit in "free" HCl is overcome. Similar studies with cow's milk yielded like results. Finzio concludes, therefore, that in infancy peptic digestion and splitting of albumin takes place in the absence of "free" HCl, and that "combined" HCl must play a part in gastric digestion.

Finzio[10] has studied also the peptic digestive capacity of the gastric content of infants after a fictitious meal; that is, after sucking on a dry or nonlactating breast, and found in all cases that the after content of the stomach digested casein. When, however, the infants were given an actual nursing of milk, the gastric contents withdrawn a half hour after nursing showed no power to digest casein. When the fluid was withdrawn one hour after nursing, that from five out of ten cases digested casein, and at one and a half hours, that from nine did so.

MISCELLANEOUS

A number of writers have reported studies on the content of the blood of infants and children in uric acid, sugar, lipase, epinephrin, and other substances. E. Liefmann[11] has studied the uric acid content of children's blood. It was quite recently a debated question whether uric acid was present in the blood of healthy adults. With the introduction of newer methods of examination it has been found that the blood of healthy adults always contains a trace of uric acid. Bass and Wichowsky,[12] using a modified Ludwig-Salkowski method, found the blood of normal adults on a purin-free diet contains 1 to 2 mg. of uric acid per 100 c.c. of blood. Other workers, using colorimetric methods, have confirmed these results. When the diet contains purins, the uric acid level may rise normally to 3 mg. Occasionally the blood of apparently healthy individuals yields values that exceed the normal. In gouty individuals the content of the blood in uric acid rises to 5 to 6 mg. No studies appear to have been previously made on the blood of infants and children.

Liefmann employed an Autenrieth-Konigsberger colorimeter. His study was undertaken primarily to determine whether children with the symptoms of the exudative diathesis (Czerny) differ from normal children in the uric acid content of their blood. He examined six normal infants and four children (ages 14 months, 2½ years, 8 and 13 years). The infants were receiving a purely milk diet.

The blood of infants was found to contain 1.3 to 1.7 mg. of uric acid of 100 c.c. of blood. In the older children the values rose slowly

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[10] Finzio, G.: Sulla digestione della caseina nello stomaco dei lattanti, La Pediatria, 1915, **23,** 95.

[11] Liefmann, E.: Ueber den Harnsäuregehalt des Kindlichen Blutes, Ztschr. f. Kinderh., 1915, **12,** 227.

[12] Bass and Wichowsky: Wien. klin. Wchnschr., 1912, **25,** 1863.

(1.7, 1.8, 2.0 and 3.7 on mixed diet, respectively), until they reached the normal values for adults on mixed diet, 3.8 to 4.6 (Steinitz). Two nursing women examined showed no increase of uric acid content — 2.0 and 3.8.

The addition of thymus broth to the diet of milk-fed infants caused a prompt rise in the uric acid content of the blood, and the higher value diminished gradually after a return to a purin-free diet. Administration of atophan, ¼ gm., to infants with a normal concentration of uric acid in their blood caused a prompt reduction of this amount (to a trace), and the effect persisted fifty or more hours. Administration of "protojuret" caused, on the other hand, an increased concentration of uric acid. The occurrence of leukocytosis from any cause had a similar effect. Liefmann was unable to find any evidence of a relation between the so-called exudative diathesis and the uric acid (rheumatic) diathesis.

Heller[13] has investigated anew the sugar content of the blood of newly born and premature infants. Goetzky, Bang, and Windelöw and Mogwitz concluded that the blood sugar of nurslings shows the same normal values and variations as that of adults. Heller studied the matter with reference to the age, birth weight, and food intake of infants. The physiology of the newly born presents so many variations from that of older children and adults that certain differences in the sugar content of the blood might have been anticipated. Heller's studies on twelve full-term newly born infants and three premature infants show that no difference exists. He employed Bang's method of estimating the sugar content of the blood.

Goetzky[14] employed Bang's micromethod on 100 normal infants and young children. He found the average percentage of sugar in the blood of twenty-three children between the ages of 2 and 12 years to be 0.102, the extremes being 0.087 and 0.118. More recently Bass,[15] in the examination of the blood content of twenty-six normal children, ranging in age from 2 to 14 years, found an average of 0.089. He employed the Benedict-Lewis method and examined the blood from two and a half to three hours after breakfast. He found that neither age nor sex seemed to influence the sugar content.

Heller concluded that the reduction value of the blood of normal newly born and premature infants lies within the same range of physiologic variation as those of older nurslings and adults. Also that the nature of the food (colostrum, breastmilk, and cow's milk in one-third dilution) has no noteworthy influence on it.

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[13] Heller, Fritz: Der Blutzuckergehalt bei neugeborenen und frühgeborenen Kinder, Ztschr. f. Kinderh., Orig., 1915, **13,** 129.

[14] Goetzky, F.: Der Physiologische Blutzuckergehalt beim Kinde nach der Mikromethode von Bang, Ztschr. f. Kinderh., 1913, **9,** 44.

[15] Bass, Murray H.: The Sugar Content in the Blood in Childhood, Am. Jour. Dis. Child., 1915, **9,** 61.

Zamorani[15a] studied the contents of the children's blood in lipase. He employed the method of Rona and Michaelis (tributyrin) and determined the content in lipase of ninety-two specimens of blood from sixty-four children of various ages, and five adults. He used 0.25 and 0.5 c.c. of serum and examined it twelve to twenty-four hours after its withdrawal. Control studies showed that the presence or absence of hemolysis had no appreciable effect on the lipolysis. Zamorani found that while the content of the blood in lipase showed individual variations, there was no noticeable difference between specimens from normal nurslings, other children and adults. No specimen was entirely lacking in lipase.

While changes in the general bodily condition of a patient may, in some instances, be accompanied by a rise or fall in the content of the blood in lipase, there are no changes that are constant or that are characteristic of any particular disease. No variations from the normal were found in certain cases of tuberculous meningitis, or in children with acetonuria. It seems that disturbances of the fat metabolism, in contrast with those of the sugar metabolism, do not lead to excretion of the fat as such, though in some conditions the fat is not fully oxidized and appears in the urine as ketones. Zamorani opposes the view of Mellis-Schirm that in diseased conditions of the lymphatic system one may draw prognostic inferences from the content of the blood in lipase; and also the contention of Samelsohn that diminished fat splitting power of the blood of atrophic infants is a cause of the disease. It appears to him but a part of a general disturbance of the body.

S. Cannata[16] studied the occurrence of epinephrin in the blood of the newly born. He examined the blood of thirty-one infants, 3 hours to 6 days old, and employed Spolverini's modification of Ehrmann's method of detecting the presence of epinephrin. This method utilizes the iris of an isolated frog's eye, and is thought to detect epinephrin in dilutions of 1:20,000,000. Cannata found that the content of epinephrin in the blood of the newly born is so little that it is not detected by this test. This would correspond to the anatomy of the suprarenal gland in infancy, the cortex being well developed, the medulla scanty.

Schlutz and Pettibone[17] have made quantitative determinations of the nonprotein nitrogen in the blood of the newly born. Previous studies appear to have been confined to the blood of human adults and lower animals. Schlutz and Pettibone studied the conditions in a series of twenty-six infants varying in age from a half hour to 10 days. The total nitrogen, urea, ammonia, and amino-acid nitrogen of the blood were determined quantitatively. By nonprotein nitrogen is meant the nitrogen that is not precipitated by methyl alcohol and zinc chlorid (Folin's method). The source of the nonprotein nitrogen is almost entirely from the proteins ingested by the organism. The recent work of Folin and Van Slyke, and others, seems to indicate that ingested proteins are completely hydrolyzed in the digestive tract, and that most of their amino-acids are thus set free and are absorbed into the blood stream unchanged and thence taken up by the tissues.

[15a] Zamorani, V.: Sul contenuto in lipasi del sangue nell'eta infantile, La Pediatria, 1915, **23,** 401.

[16] Cannata, S.: Sulla presenza di adrenalina nel sangue del neonato, La Pediatria, 1915, **23,** 244.

[17] Schlutz, F. W., and Pettibone, C. J. V.: Quantitative Determinations of Nonprotein Nitrogen in the Blood of the New-Born, Am. Jour. Dis. Child., 1915, **10,** 206.

Older methods showed that 100 c.c. of normal adult human blood contained as a maximum 50 to 70 mg. of nonprotein nitrogen. Newer methods show lower maximum figures. Folin and Denis[18] report a maximum of 22 mg. per 100 c.c. of blood. Of this the larger part is urea nitrogen — 11 to 13 mg. The percentage of both is at any given time higher in the portal blood than in the general systemic blood.

Schlutz and Pettibone find that the total nonprotein nitrogen per 100 c.c. of infants systemic blood is approximately the same as in the adult. Also that the age and weight of the infant and the period after feeding have no bearing on the total. The percentage of urea nitrogen is uniformly high and averages about 50 per cent. of total nitrogen.

The probable source of the amino-acids in the blood of the infant just born, or before the first feeding, lies in the placental circulation.

Tileston and Comfort[19] made a similar study on children suffering from pathologic conditions. Because of finding considerable variations when the specimens were taken just before the noon meal, they were led to take the blood, in the case of children over 2 years of age, before breakfast, after a fast of twelve hours or more. In the two normal cases studied in this manner there were 24.4 and 26 mg. of nitrogen, and 9.8 and 10.9 mg. of urea nitrogen, respectively. In children who are acutely ill and taking in consequence less than the accustomed amount of food, they found the blood might be taken at any time without the liability of error.

Fenger[20] and Pellegrini[21] studied the iodin content of the thyroid in the young. Pellegrini found that iodin was present in about two thirds of the twenty-three cases examined by him; that the age had no effect on the quantity; and that iodin might be absent in large glands and met with in small ones.

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[18] Folin and Denis: On Uric Acid Urea and Total Nonprotein Nitrogen in Human Blood, Jour. Biol. Chem., 1913, **14**, 29.

[19] Tileston and Comfort, C. W.: The Total Nonprotein Nitrogen and the Urea of the Blood, and the Phenolsulphonephthalein Excretion of Children, Am. Jour. Dis. Child., 1915, **10**, 278.

[20] Fenger, F.: On the Presence of Iodin in the Human Fetal Thyroid Gland, Jour. Biol. Chem., 1915, **15**, 695.

[21] Pellegrini, R.: Sul contenuto in iodio delle ghiandole tiroidi dei feti, dei neonati e dei bambini, Riv. di Clin. Pediat., 1915, **13**, 195; abstr., Jahrb. f. Kinderh., 1915, **32**, 174.

Sedgwick[22] examined anew the question of oxalic acid excretion in the urine of children. Little work has been done on this. Aron and Franz concluded that the urine of infants contains small amounts of oxalic acid almost without exception. This was true even when an oxalic-acid-free diet was given. The addition of sugar, dextrimaltose or starchy matter to the diet was followed by a somewhat higher excretion. Sedgwick used the Albahary method of determining oxalic acid. He finds that newly born infants excrete oxalic acid in the urine in varying amounts up to 9 mg. per day, and that older children excrete considerable quantities. If the usual figures given for the excretion of oxalic acid in adults — 15 to 20 mg. (Neuberg) — are accepted, the excretion in children is relatively, and at times absolutely, higher.

Taylor[23] made an experimental investigation of the occurrence of creatin in the urine of children. Some years ago W. C. Rose noted the constant occurrence of creatin in the urine of children until about the age of puberty. This observation was later verified by Folin and others. The closely related compound ceratinin appears normally and constantly in human urine; creatin appears in the urine of adults in various forms of carbohydrate starvation and in severe forms of diabetes. It has been suggested that its appearance in the urine of childhood is due to a relative deficiency of carbohydrate in the diet. Taylor, however, finds that creatin continues to appear in the urine of children in spite of a high intake of carbohydrate. The sum of the creatin plus the creatinin in the urine of children compares approximately with the sum of the two constituents in the adult when due allowance is made for the weights of the individuals and the probable amounts of muscular tissues. These findings may reasonably be ascribed to an incomplete conversion of creatin into creatinin by the developing organism.

Veeder and Johnston[24] have examined the urine of twenty-one normal children for the presence of ketones and betahydroxybutyric acid. The results were so consistent that it seemed unnecessary to examine a larger number. The children ranged in age from 2 months to 12 years, and were receiving a standard diet of sufficient caloric value to cover the needs of children at light work or play. They were in bed, were afebrile, and had been on a standard diet for several days before the twenty-four hour specimen of urine was collected for examination. The methods of Schaffer and Messinger were used.

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[22] Sedgwick, J. P.: Oxalic Acid Excretion in the Urine of Children, Am. Jour. Dis. Child., 1915, **10,** 414.

[23] Taylor, A. E.: On Creatinuria, Jour. Biol. Chem., 1915, **21,** 663.

[24] Veeder, B. S., and Johnston, M. R.: Presence of Ketones and Betahydroxybutyric Acid in the Urine of Normal Children, Am. Jour. Dis. Child., 1916, **11,** 291.

When the caloric values of these children were fully covered by the diet, small amounts of ketones and betahydroxybutyric acid were always found. The amount was small and varied from 20 to 100 mg. in terms of acetone in twenty-four hours, the amount excreted being 50 to 80 mg. As a rule, the amount of betahydroxybutyric acid was somewhat greater than the amount of other ketones, but this did not always hold true. The age, sex and body weight of the child had apparently no effect on the amount excreted. It would seem thus that the large amounts of acetone bodies that appear in the urine in febrile conditions and in restricted diets represent an increased excretion of substances normally present, rather than the appearance of abnormal substances.

THE INITIAL LOSS OF WEIGHT IN THE NEWLY BORN

The analysis of this phenomon by Benestad has recently been reviewed in this journal. Benestad viewed the initial loss of weight in the newly born as a physiologic condition, and spoke of the failure of all efforts to prevent the loss, or even to appreciably diminish it, by supplying newly born infants with milk from wetnurses whose children are but a few days older than the patient, as seeming to indicate a functional inability to utilize milk during the first days of life, even in a mature infant. Altherr's work seemed to show that forcing food at this time might even delay the normal recovery of the birth weight. Another attempt to prevent this initial loss of weight is now reported.

B. Schick[25] of von Pirquet's clinic has attempted to prevent the usual (physiologic) loss of weight in twelve infants. He states that there are exceptional infants who do not show this usual early loss of weight, and that there are well-established observations that subsequent children show less rapid and less prolonged initial loss of weight than first-born children. This is attributed to an earlier onset of the breast secretion in the multiparous breast. Early and more frequent application of the child to the breast is also said to be helpful. Recent studies by Jaschke and V. Reuss, embodying many cases, are cited as showing that the giving of indifferent fluids, or of woman's milk, may lessen the loss.

Schick attempts to prevent the loss entirely. He assumes that the initial loss of weight is due to insufficient supply of food, and that even where an abundant supply is at hand, the newly born infant cannot avail himself of it, because of his inability to nurse properly — the infant is not born with a *fully* developed ability to nurse, he must *learn* to nurse; this he usually does in a few days. In the meantime Schick attempts to give a total amount of nourishment that will approximate the infant's needs, as computed from what is known of the needs of infants of greater age.

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[25] Schick, B.: Zur Frage der physiologischer Körpergewichtsabnahme des Neugeborenen, Ztschr. f. Kinderh., Orig., 1916, **13**, 257.

The optimum amount of (breast) milk for an infant from the second to the ninth month of his life, is, according to von Pirquet, 15 per cent. of the body weight, and the minimum, or mere maintenance ration, is 10 per cent. of the body weight. This 10 per cent. Schick attempted to give each infant during every twenty-four hours. In calculating the amount to be supplied, he allowed for the greater calorific value of mother's milk during the first week of nursing, as compared with later production. Only after the third day of life was the total amount of food received by the infant, breast feeding plus forced feeding, allowed to approach 15 per cent. of the body weight.

By this procedure Schick was able to prevent the initial or physiologic loss of weight in all cases. The infants are said to have held their weight, or gained slowly, during the first two or three days, during which time they were giving off their "dead ballast," meconium, swallowed amniotic fluid, etc., and then to have gained rapidly and well. During the first hours, vomiting of the ingested amniotic fluid disturbed the process of forced feeding in some instances — this vomiting may occur whether fluid be forced or not — but this soon ceased under continuance of the forced feeding. No injury to the children of any kind was discernible.

The practical difficulty of Schick's procedure lies, first, in the time required for such frequent forced feedings as he thought necessary — they were given every hour or so because of the large amount of fluid to be ingested during twenty-four hours — and second, in the difficulty in procuring sufficient mother's milk from women whose children are not more than 1 week old. From a purely theoretical point of view the work is of much interest.

BREAST SECRETION AND GENITAL BLEEDING IN THE NEWLY BORN

The occurrence of transitory swelling of the breast and the appearance of a mammary secretion (witch's milk) in the newly born has been known from the earliest times. The occurrence of the more infrequent phenomenon of genital bleeding in the newly born female infants has been known for a century or more. It has recently attracted scientific attention anew. Von Zappert[26] (1903) first described in a precise manner the pathologic anatomy of the uterus in such a case. Halban[27] extended these studies in the next year.

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[26] Von Zappert: Ueber Genitalblutung neugeborener Mädchen, Wien. med. Wchnschr., 1903, **53**, 1478.

Clinically, the phenomenon seems to occur in 0.12 to 2.5 per cent. of all newly born female infants; histologic examination of the uterus, in a limited number of infants, shows that it appears in a much higher percentage of 8.3 to 38 per cent.

Zacharias[28] has recently examined 400 newly born female infants in Professor Zweifel's clinic. He found that genital bleeding occurred in 2½ per cent. of these infants. The bleeding occurs most frequently in large, heavy, full-term infants. It is not more common in first children than in later ones. Commonly the bleeding occurs drop by drop. It may be so slight as readily to escape notice, or it may be profuse enough to cause alarm in the mother or nurse. The bleeding usually occurs on the sixth or seventh day, but may appear later, rarely earlier. It is accompanied in many cases by an increased output of mucus, clear and fluid at first and later blood stained. This was not seen in Zacharias' cases. Often on the second day a small bloody fleck was noticeable at the vaginal outlet. It gradually became darker. The bleeding lasted one to three days. In no case was it accompanied by any signs of a general constitutional disturbance.

Von Zappert[26] recognized the uterus as the source of the blood. He found the muscular layer presented no special change, but that the blood vessels in the submucous tissue were overfilled and dilated, and in certain places he was able to demonstrate the actual escape of red blood corpuscles. The overlying epithelium was uninjured. There was no evidence of infection.

Halban[27] found that while the uteri of infants dying between the ages of 3 weeks and 2 years averaged 2.5 cm. in length, the uteri of eleven newly born infants averaged 3.2 cm. in length. Bayer (1902) had found that the uterus of newly born infants is larger than that of older infants, reaching sometimes ten times the volume found later in the first year. He found the following averages: seventh to ninth month of fetal life, 3 cm.; full-term newly born, 3.7 cm. (limits 4.2 and 4.5, Roderer). Halban found that the relatively large uterus of early infantile life gradually returns to normal size. This change is completed in about twenty-eight days after birth, and the process is termed by him "puerperal involution of the fetal uterus." Histologic study of the ovaries shows that they are entirely quiescent.

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[27] Halban: Schwangerschaftsreaktion der fötal Organe und ihre puerperal Involution, Ztschr. f. Geburtsh., 1904, **53,** 191; Ueber fötale Menstruation und ihre Bedentung, Kongressbl. f. Gynekol., 1904, **28,** No. 2, p. 1270. Reference from Zacharias, Footnote 28.

[28] Zacharias, Erich: Genitalblutung neugeborener Mädchen, Med. Klin., 1914, **10,** 1645.

Zappert viewed the whole process as a phenomenon of a physiologic rather than a pathologic nature. Halban extended this conception and advanced a new theory for the occurrence of genital bleeding in the newly born by suggesting that it was due to the action of some substance derived from the maternal placenta, circulating in the blood and acting as an internal secretion. The infantile uterus seems to become sensitive to such a substance in the eighth or ninth month of intrauterine life. This conception has found some experimental basis. Zacharias thinks that the mechanical factor of pressure on the abdominal organs during the birth of unusually large female infants may become a factor by predisposing the oversensitive uterus toward bleeding.

Clinically, the prognosis is always good, and the diagnosis alone is of interest. Inspection of the parts will usually reveal the source of the bleeding. Feer recommends the use of a small ear speculum. Congenital papillomatous growths of the vulva and vagina must be considered, also polyp-like prolapse of the urethral mucous membrane, with bleeding (Langstein), and congenital tumors with uterine bleeding. Much more common is sepsis with bleeding from the genital mucous membrane.

PATHOLOGY

During the past year there have appeared a considerable number of isolated reports of pathologic conditions in infants and children. A number of these will be referred to here. There have appeared also a few reports of a more extensive or monographic nature.

A paper of the latter type is a report by A. S. Warthin[29] of a study on the occurrence of malignant neoplasms in the young. Warthin's analysis tends to controvert the current statement that carcinoma is a disease of the old, and sarcoma of the young. It seems that the majority of these statements are derived from the writing of the Virchow period "when no exact differentiation of carcinoma and sarcoma was made, and when malignant teratoid tumors were classed as sarcoma or carcinoma, or chondroma, etc., as the case might be, according to the preponderance of one or the other of the elements making up the growth." The correctness of the diagnosis in many of the congenital and early life tumors is now in question, and so are, consequently, the generalizations based on them.

Warthin's material is a homogeneous one, derived almost entirely from the population of a single state, Michigan, and representing the average population of that state. The possibility of error in diagnosis is reduced to a minimum by the material having been utilized both for purposes of practical diagnosis and for the teaching of pathologic histology.

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[29] Warthin, A. S.: The Occurrence of Malignant Neoplasms in the Young as Shown by an Analysis of 2,000 Cases of Malignant Neoplasm Examined in the Pathological Laboratory of the University of Michigan, Arch. Int. Med., 1915, **15**, 444.

In a total of 2,000 cases of neoplasm, Warthin found thus that 36 appeared before the age of 13 years (109 appeared in the next thirteen years). There were 33 cases of sarcoma, 2 cases of carcinoma, 1 in the fourth and 1 in the eleventh year; and 1 malignant teratoma. "The large number of cases in the first year emphasizes the importance of the congenital factor," says Warthin, and the influence is felt in the case of the majority of the tumors up to the period of sexual ripeness, even when no actual evidences of a teratoid nature could be demonstrated in the tumor. Sarcoma predominates in the period of infancy and childhood, but the parallel increase of both sarcoma and carcinoma with age (this is seen principally after the thirteenth year in the present series) is noteworthy, and in contradiction to the usual belief that sarcoma is essentially a disease of childhood.

Cases of malignant teratomas fall in the period of early childhood and developing sexual life, those of the testis and ovary, particularly, developing in the latter period.

Williams[30] pointed out the relative frequency of retinal gliomas and renal tumors in infancy and early childhood. No retinal gliomas appear in Warthin's series. Williams' work was based on Duzan's analysis of 182 malignant tumors of early infancy, Picot's analysis of 424 cases, his own of 56 consecutive cases. Poinset's 25 cases of bone sarcoma in infancy, Gross' study of sarcoma of the long bones (51 cases) and 41 cases tabulated by Butler and Colby. Warthin's conclusions agree in the main with those of Williams, and his view of the congenital or teratoid origin of malignant neoplasms in infancy and early life is supported. "Malignant tumors are relatively rare before puberty, but there is a steady ascending line of occurrence from childhood onward to middle life, both sarcoma and carcinoma showing a parallelism of occurence."

Hansell[31] has reported a case of bilateral glioma of the retina in a child of 2 years. He refers to Wintersteiner's classical monograph (467 cases) on nonpigmented cancer of the retina, and to the later studies of Wehrli, Lindenfeld, Fuchs, and others. Seventy-five to 80 per cent. of the cases occur in the first three years of life, and most within the first two years of life. About 24 per cent. of the cases are bilateral. Clinical histories emphatically negative the supposition that the other eye is involved sympathetically.

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[30] Williams, W. R.: The Natural History of Cancer, New York, 1908.

[31] Hansell, H. F.: A Case of Bilateral Glioma of the Retina, Am. Jour. Dis. Child., 1915, **11,** 485.

Williams[32] reports an instance of infiltration of the heart by large round-cell sarcoma in a boy of 8 years. Symptoms were of thirteen weeks' duration, pain in the left shoulder-joint, cough and much expectoration, with later vomiting, swelling of the eyelids and orthopnea. There were no enlarged veins.

Necropsy showed the anterior mediastinum filled with a hard white growth. This was adherent to the sternum, invaded the diaphragm, obliterated the pericardial space, enclosed the heart in a hard growth, and invaded the cardiac cavity. The mitral valve was thickened and appeared to be infiltrated. There were scattered growths in both pleurae. There was no enlargement of either the cervical or axillary glands. Microscopic examination showed the growth to be a large round-cell sarcoma, probably originating from the sternal periosteum.

Primary malignant growths of the pericardium are exceedingly rare; secondary growths arising in the mediastinum are scarcely more frequent. An instance is known in which the left ventricle was almost entirely invaded by the new growth.

ANOMALIES OF THE CARDIOVASCULAR SYSTEM

K. Secher[33] has described an instance of persistence of the primary paired longitudinal veins of the embryo. The condition was found at necropsy, in a 1½-year-old girl. There was aplasia of the left kidney, with hypertrophy of the right kidney and the left suprarenal gland. The external genitalia and the ovaries were symmetrically developed on the two sides, but the fallopian tube and the left horn of the uterus were smaller on the left than on the right side.

In place of one large vena cava inferior there were present two vessels which united to form one at a level just above that of the hilus of the persistent and hypertrophied right kidney. These two vessels Secher interpreted as persistent venae cardinales.

An instance of complete situs inversus is reported by Spallica.[34]

Moffett and Neuhof,[35] in a clinical report of congenital dextrocardia in a 3½-year-old boy, in whose case no necropsy was permitted, give a list of those cases of pure dextrocardia reported to date, 151 cases in all. The term "pure dextrocardia" is used here to signify those cases of dextrocardia in which the liver and spleen are normally placed. Moffett and Neuhof find no theory sufficiently convincing to explain all cases. The most prominent of the theories concerning the origin of pure dextrocardia is that in the prenatal development of the heart the right side develops more rapidly than the left and pulls the heart to that side.

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[32] Williams, E. C.: Infiltration of the Heart by a Large Round-Celled Sarcoma, Brit. Jour. Child. Dis., 1916, **13,** 114.

[33] Secher, K.: Ueber Aplasia renis Venae cardinalis persistentes, Berl. klin. Wchnschr., 1915, **52,** 487.

[34] Spallica, A.: Su di un caso di situs viscerum inversus totalis, Riv. di Clin. Pediat., 1915, **13,** 185.

[35] Moffett, R. D., and Neuhof, S.: Congenital Dextrocardia with Patent Interventricular Septum, Am. Jour. Dis. Child., 1915, **10,** 1.

Morse[36] reports a case of congenital anomaly of the heart in a 9-year-old boy. The child was first seen when 4 years old and was observed thereafter until his death. The picture was that of congenital heart disease, but no murmurs were detected, it is said, until a few months before his death, at which time subjective symptoms first developed.

The malformation with which it was thought the clinical symptoms were reasonably consistent were absence of the ventricular septum, transposition or irregular origin of the great vessels and pulmonary artery, with some secondary malformation. Postmortem examination of the heart revealed complete congenital atresia of the pulmonary artery, congenital defect of the interventricular septum, corresponding to the membranous portion, persistent ductus arteriosus, patent foramen ovale, dilatation and hypertrophy of the right ventricle, acute vegetative endocarditis, and thrombosis of the ductus arteriosus. Illustrative photographs accompany the report.

GASTRO-INTESTINAL TRACT

Chiari[37] has described an instance of infection of a congenitally syphilitic infant with hyphomycotic fungus. The infant died at 10 days of age, and at necropsy showed the usual evidences of congenital lues and a purulent peritonitis in the exudate of which probable colon bacilli were found. In addition to these lesions, there was present on the anterior wall of the stomach between the cardia and pylorus a circular, blackish discoloration of an area of about 5 square centimeters, with a yellowish center. The lesion extended through the thickness of the walls. On the inner surface there was a pea-sized loss of substance. The outer surface was bound to the liver by a fibrous exudate. Staining of the tissue, especially with carbolfuchsin, revealed numerous threads of a hyphomycete. Occasional masses of bacilli, apparently colon bacilli, were also seen. The threads of the fungus measured 6 to 10 microns in breadth.

Cases of similar infections, always of the stomach, have been described by Marchand (1910, 18-year-old girl); Benche (1911, 33-year-old man); Benilli (1912, 36-year-old woman), and Ljubimowa (1913, 64-year-old woman). The lesion appears as a small, sharply-defined area that in its dark gray color stands out sharply against the background. Where such areas are found, hyphomycotic infection should be thought of and examination for fungi should be made through cultural and staining methods.

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[36] Morse, J. L.: A Case of Congenital Heart Disease with Demonstration of Specimen, Am. Jour. Dis. Child., 1915, **10**, 27.

[37] Chiari, H.: Hyphomycosis ventriculi, Wien. med. Wchnschr., 1915, **65**, No. 1, p. 282.

A number of cases of congenital and other abnormalities of the gastro-intestinal tract have been reported.

Strauch[38] has described an instance of mesenterium commune with abnormal course of the jejunum found in dissecting the body of a 1-year-old boy. The condition was evidently a pure congenital anomally.

On opening the abdomen, loops of small intestine presented themselves, entirely covering the colon ascendens and transversum, with the exception of the hepatic flexure. On raising these loops of small intestine the cecum with the appendix was found in the region of the lower pole of the left kidney where they were completely and freely mobile. The colon ascendens passed from here upward to the hepatic region and was entirely free and mobile and without any fixation to the posterior abdominal wall, and had a long mesentery in common with the ileum and colon transversum.

The duodenojejunal flexure was not at its normal site nor in its proximity, but lay in a more dorsal plane behind the plate of the mesocolon commune, whence the jejunum emerged in an abnormal fossa and ran downward along the vertebral column. The sigmoid flexure was elongated, and even considering the age possessed a wide range of mobility. The course of the arteria mesenterica superior was abnormal.

The condition finds its explanation in disturbance of the normal rotation of the originally free umbilical loop and the normal coalescence of the mesenteries and the intestinal segments with the posterior abdominal wall. Instances of failure of rotation have been reported by Mayo[39] and others; while rotation of the primitive umbilical loop in the reversed direction results in situs inversus intestini, which may be more or less incomplete. The occurrence of such conditions is of interest from the standpoint of embryology, teratology and operative surgery. Boyd[40] has recently considered this in relation to appendectomy and the performance of gastroduodenostomy.

Holmes[41] has reported an instance of congenital obliteration (atresia) of the extrahepatic bile ducts. The child, a 7-weeks-old boy, presented the usual clinical picture, and died at 15 weeks of age. The gallbladder was atrophic, the arrangement of the hepatic ducts was anomalous, in that they opened independently into a small globular chamber; the cystic and common ducts were obliterated through the greater part of their course. The pancreas, its ducts, and the duodenal papilla were normal. There were no evidences of any inflammatory origin, and the condition seems most readily explained as an anomaly of development.

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[38] Strauch, August: Mesenterium Commune with Abnormal Course of Jejunum, Am. Jour. Dis. Child., 1916, **11,** 208.

[39] Mayo, C. H.: Med. Rec., New York, 1912, **81,** 401.

[40] Boyd, S.: Brit. Med. Jour., 1914, **2,** 507.

[41] Holmes, J. B.: Congenital Obliteration of the Bile Ducts; Diagnosis and Suggestions for Treatment, Am. Jour. Dis. Child., 1916, **11,** 405.

Holmes reviews the literature of the subject and presents diagrams showing the nature and extent of the lesions in the 120 odd cases reported to date. It appears that diagnosis can usually be made and that operative relief is anatomically possible in at least 16 per cent. of all cases. The technical difficulties have already been in great part overcome.

Drennan and Clark[42] report a case of multiple complete congenital obstruction of the intestine in an infant. Aside from imperforate anus, congenital obstructions of the intestine are infrequent. The small intestine is more often involved than the large intestine. According to Leichenstein,[43] the proportion of congenital malformations of the intestine is as follows: 375 at the anorectal junction, 75 in the small intestine and 10 in the colon. In the small intestine, atresia is more often seen than stenosis. The common site is in the duodenum. Usually but one point of actual obstruction is found; beyond these one or more points of stenosis are sometimes found. Few if any cases of complete multiple congenital obstructions of the jejunum have been previously reported.

Drennan and Clark's case was a 4-day-old white boy. He began to vomit as soon as he was put to the breast. This was repeated after every feeding. The vomited matter was bile-stained mucus and milk. Enemas were unproductive. Laparotomy revealed a high congenital malformation of the intestine and also points of stenosis. Necropsy revealed four complete congenital occlusions of the small intestines. "The first one was 28 cm. from the pyloric ring, and the form of occlusion was that of a thin tissue diaphragm lined on its upper surface by the usual type of mucous membrane, while below it had a smooth parchment-like surface. The duodenum and the portion of the jejunum above this partition had been a large food reservoir for all the food taken, and therefore was tremendously dilated and the wall thickened." The second obstruction was found 15 cm. below this, the bowel simply tapered off to a solid cord of tissue, 3 to 4 cm. in length and 1 mm. in thickness; the lumen above contained only clear mucous fluid. A third obstruction, 10 cm. below this, was similar in nature. The fourth obstruction occurred 42 cm. below the third and was a membranous partition like the first one. A small persistent foramen ovale was the only other congenital malformation found in the body.

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[42] Drennan, L. M., and Clark, H. C.: A Congenital Malformation of the Intestine; Multiple Points of Complete Obstruction, Am. Jour. Dis. Child., 1915, **10**, 360.

[43] Leichenstein, in Osler's Modern Medicine: Lea & Febiger, Philadelphia and New York, 1908, **5**, 458.

W. P. Erus[44] reports a case of congenital infrapapillar atresia of the duodenum that was corrected surgically by anastomosis.

O. Sachs[45] reports a case of dilatation of the large bowel, simulating Hirschsprung's disease, that occurred in a 7-year-old boy who had suffered from constipation from birth. Examination showed an anal aperture of small diameter, ¼ cm., and fibrous margin. At operation this was found to admit to a fibrous passage about 4 cm. long, which led to a much dilated rectum filled with stony, hard fecal masses. A plastic operation brought temporary relief and further surgical treatment completed the cure. The symptoms of Hirschsprung's disease disappeared entirely and the abnormality of the large intestine was clearly the result of anal stenosis alone.

Sachs calls attention to other analogous cases in the literature; for example, a month-old infant in whom a small congenital angiomatous tumor and a fissure led to dilatation and hypertrophy of the colon; another in which a smooth, circular, subcutaneous congenital fibrous band led to anal stenosis, and secondarily to dilatation of the colon; and also one in which the use of ordinary soap as a suppository led to severe irritation of the anus and rectum, fibrous stenosis, and secondary changes above.

An instance of congenital atresia of the colon is mentioned by Rivarola.[46] No details are given.

Conciliis[47] reports a case of multilocular lymphatic cysts of the mesocolon in a 9-year-old boy. Symptoms had appeared fifteen days before. The child had been seized with violent abdominal pain, and a tumor became evident in the epigastrium and left hypochondrium. Previously he had been well; thereafter purges were required. An incarcerated umbilical hernia was thought of. Operation revealed multiple cysts of the mesocolon, ranging downward from the size of an orange. According to Conciliis, these tumors would be considered multilocular lymphatic cysts by the clinician. The pathologist would regard them, histologically, as cystic or cystoid lymphangiomas (Wegener). Such cysts of the mesocolon are not common. Deaver, in 1909, was able to collect only 134 cases from the literature.

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44. Erus, W. P.: Hospitalstid., Oct. 27, 1915.

45. Sachs, Otto: Ein Fall Einer Analstenose, einen echten Hirschsprung's vortauschend, Jahrb. f. Kinderh., 1915, **81,** 469.

46. Rivarola: Societa Argentina di Pediatria, La Pediatria, 1915, **23,** 618.

47. De Conciliis, Ugo: Cisti linfatica mulilocul are del mesocolon in un bambino, La Pediatria, 1915, **23,** 643.

Bythell[48] reports an instance of hernia of the stomach through the esophageal opening in the diaphragm. The previous history consisted of attacks of persistent vomiting for about six months, the condition steadily getting worse. Apparently there was never at any time much abdominal pain. On exploration, the major part of the stomach was found to be herniated through the esophageal opening. The other abdominal organs were normal. The stomach was brought down and stitched to the anterior abdominal wall. It later escaped. At a second operation a gastrostomy was done.

Volpe[49] reports a case of congenital defect in the diaphragm which permitted the terminal portion of the duodenum, the small intestine, the cecum, appendix, and much of the colon to pass up into the left side of the thorax. The infant presented a normal appearance at birth, but remained cyanotic, and soon died. Volpe considers this anomally at some length and presents a full bibliography. Nau has classified such cases as (1) those in which the separation of the pleural and peritoneal spaces, originally one in early embryonic life, is never completed, and (2) those in which a defect in the musculature or fibrous tissue of the diaphragm permits a sacculated hernia upward. Volpe's case was of the first type.

Another case is reported by R. Monti.[50]

CENTRAL NERVOUS SYSTEM

Strauch[51] has reviewed the subject of pachymeningitis hemorrhagica interna in infants. Summarizing various theories and certain experimental work, he concludes that pachymeningitis hemorrhagica interna as it occurs in infancy is most probably an infectious disease, caused by the meningococcus or other organisms. The meningococcus and other organisms may produce now leptomeningitis, now pachymeningitis; the two processes may be more or less combined in certain cases. The early observations of Weichselbaum[52] would tend to confirm this view, as would also recent studies of Rosenow.[53]

His own case was a purely clinical one, no necropsy being granted. Lumbar puncture at different times yielded a large gram-negative coccus that was characteristically agglutinated by serums containing

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48. Bythell, W. S. G.: Hernia of the Stomach Through the Diaphragm in a Child Aged 9 Years, Brit. Jour. Child. Dis., 1915, **12,** 236.

49. Volpe, Carlo: A Proposito di un caso di erniä diaprammatica congenita in un neonato, Riforma med., 1915, **31,** 1125.

50. Monti, R.:. Wien. klin. Wchnschr., 1915, **31,** 1125.

51. Strauch, A. B.: Am. Jour. Dis. Child., 1916, **11,** 23.

52. Weichselbaum, A.: Ueber die Aetologie des akuten Meningitis cerebrospinale, Fortschr. d. Med., 1887, **5,** 620.

53. Rosenow, E. C.: Jour. Infect. Dis., 1915, **16,** 240; ibid., **16,** 367; ibid., **17,** 219.

specific agglutinins (serum from a patient convalescent from epidemic meningitis, and antimeningitis serum in dilution of 1:60 to 1:80).

Holmes[54] has reported a case of large multiple cerebral abscesses in an infant of 23 months. The child developed symptoms of hydrocephalus at 18 months of age, and the condition progressed to death under the picture of chronic internal hydrocephalus of the obstructive type. After death two large and three smaller abscesses were found occupying the posterior half of the left cerebral hemisphere. They were apparently of pyogenic origin. But the presence of organisms could not be demonstrated. Neither the history nor the necropsy findings suggested a portal of entry. The tissue was noteworthy in the large size of the abscess cavities (6.2 by 5 by 7.5 cm.), in the unusual development of pyogenic membranes, and in the presence of numerous and well-defined examples of the so-called cerebral granule cells, or Gluge's corpuscles.

Certain phases of the literature on the subject are reviewed by Holmes. Cases of cerebral abscess occurring in infants so young as his patient appear to be exceedingly rare (Okada, Heiman). Recent experimental work (Tanaka and others) indicates that cerebral granule cells are derived from preexisting glia cells.

Smith[55] reports an instance of acute myelitis appearing two weeks after the onset of varicella, with very widespread eruption, in a 7-year-old boy. The child's recovery was still incomplete a year later.

Acute myelitis is not altogether an uncommon accompaniment of infectious diseases such as typhoid fever, malaria, scarlatina, variola, acute rheumatism, measles, dysentery, gonorrhea, pneumonia, and streptococcus and staphylococcus infection. Councilman has mentioned varicella as a cause. In Smith's case symptoms of myelitis followed so closely an infection with varicella as to justify the assumption of a definite etiologic relationship.

GENITO-URINARY SYSTEM

Losee[56] reports three cases of congenital anomaly of the kidney, one congenital hydronephrosis, one typical horseshoe kidney, and a unilateral fused kidney. The specimens were obtained from stillbirths.

The first was the size of a grapefruit and was divisible into two parts, a lobulated thinned-out cortex without any microscopic evidence of normal renal tissue, and a lower portion with a smooth, firm wall continuous with the ureter. There was a stricture in the ureter at the point where it joined the pelvis, and it varied in size throughout the remainder of its course. The cyst contained a pale, straw-colored fluid in which there was no urea present. The right kidney presented two small cysts of the cortex; its ureter entered the hilum in the normal manner.

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[54] Holmes, J. B.: Multiple Abscesses of the Brain in Infancy, Arch. Int. Med., 1916, **17,** 591.

[55] Smith, D. C. W.: Acute Myelitis Following Varicella. Am. Jour. Dis. Child., 1915, **10,** 445.

[56] Losee, J. R.: Report of Three Cases of Congenital Anomaly of the Kidney, Bull. Lying-In Hosp., 1915, **10,** 101.

Of twenty cases collected by Roberts, thirteen were bilateral. An imperforate urethra is the usual cause of these. The most common cause of unilateral congenital hydronephrosis is stricture of the ureter at its junction with the pelvis. Stricture of the ureter at its vesical extremity, kinking of the ureter, and compression of it by a supernumerary artery (Roberts), are other causes.

In horseshoe kidney the fusion is more common at the lower poles. It takes place in the fifth to seventh week of embryonic life, when the kidney is a pelvic organ. Fusion of the upper poles generally takes place after the kidney has migrated upward. The pelves are then well developed independent structures and do not fuse. According to the structure, fusion of the kidneys may be of three grades: (1) the lower poles are united by a fibrous band; (2) the bridge consists of only the cortex of the kidney, and (3) the bridge is broad and thick and consists of all the structures of a normal kidney. The anomaly occurs in 0.08 per cent. of necropsies (Morris and Socin, 16,000 necropsies).

In Losee's specimen of horseshoe kidney, the organs were united by their lower poles. The pelves of the two sides were not continuous, though that on the right side was divided into the communicating portions. Two ureters arose from the pelvis of the right kidney, one from the upper portion and one from the bridge. They ran a parallel course and united in a common orifice in the trigon. The one ureter from the left kidney took the usual course.

The specimen of sigmoid kidney, or unilateral fused kidney, represents a rarer anomaly. The kidney was diagonally located, the upper pole lying on the left side of the abdomen opposite the first lumbar vertebra, and the lower pole in the bony pelvis. The pelves were not continuous. The ureters were single, normal in size, and entered the bladder normally. That on the right entered a small hilum on the anterior surface of the inferior portion of the kidney; that on the left entered another hilum near the superior pole.

The position of the kidney and the fact that two ureters enter the bladder on different sides distinguishes the case from one of complete absence of one kidney. In the last mentioned anomaly one of the kidneys either fails to bud off from the Wolffian duct, or passes through the first stage and becomes arrested and later absorbed.

Rolleston[57] reports an instance of a single pelvic kidney, in a

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[57] Rolleston, J. D.: Single Pelvic Kidney, Brit. Jour. Child. Dis., 1916, **13,** 80.

14-year-old boy, situated on the right side within the brim of the pelvis, and lying in apposition to the posterior wall of the bladder. It was irregular in shape and reniform, and was lobulated. It measured 3¼ inches in length, and 1 inch in thickness, and varied in width from 1¾ inches at its upper part, to 2⅛ inches at its lower part, and weighed 4 ounces. The hilus was situated arteriorly, and from it issued a single ureter which was evidently dilated and hypertrophied, but at its vesical extremity barely admitted a pin's head. There was some dilatation of the pelvis and calices of the kidney, but no marked degree of hydronephrosis. No trace of a left kidney or ureter could be found. There was no malformation of the genital organs. The boy died of septic scarlet fever. He was mentally defective.

Rolleston gives much interesting historical and clinical data in his report. Single or a symmetrical kidney (renal aplasia or agenesis) is extremely uncommon, being found in only one out of 2,400 necropsies (Morris). About 300 cases, some of them doubtful, are on record. Congenital displacement of the kidney, or renal distopia, is less uncommon. Its frequency is estimated at one in five hundred (Girard) to one in one thousand (Guizetti and Pariset).

Kakels[58] reports an instance in which a large congenital hydronephrosis in an infant of 6 weeks was diagnosed with considerable certainty by the history, physical signs and Roentgen-ray findings, and successfully removed by transperitoneal nephrectomy. The child made an uneventful recovery. The sac contained nearly a liter of straw-colored fluid. The ureter was found perfectly normal throughout its whole length, with no dilatation or stricture. Its insertion into the sac was at some distance from the blood vessels, and it lay flat on the surface of the sac. Its obliquity of entrance and its anomalous position may have been an etiologic factor in the cause of the hydronephrosis.

Another case of congenital hydronephrosis is reported by Williams.[59] It occurred in a male infant of 6 months. Clinically there was marked intestinal peristalsis. The ureters could be felt on either side and the right one resembled an intussusception. There was almost complete suppression of urine. Necropsy showed both ureters the size of the small intestine and the bladder much hypertrophied. There was no demonstrable fold in the urethra to cause obstruction.

LYMPHATIC SYSTEM

Schridde[60] has considered the possibility of status thymolymphaticus being in some instances a congenital condition. He has made postmortem examinations of fifty-nine still-born infants, and finds that in fetal material, even up to full-term birth, the lymph nodes in the spleen and intestine are not visible. The tonsils are visible, but it is difficult to draw conclusions as to their size.

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[58] Kakels, M. S.: Large Congenital Hydronephrosis in an Infant 6 Weeks of Age, New York Med. Jour., 1916, **103**, 547.

[59] Williams, E. C.: Brit. Jour. Child. Dis., 1916, **13**, 50.

[60] Schridde, Hermann: Der Angeborene Status Thymolymphaticus, München. med. Wchnschr., 1914, **61**, 2161.

He finds the thymus presents the following normal range of variation in weight: fetuses, 42 cm. long, 3 to 11 gm.; 46 cm. long, 8 to 14 gm., and 47 cm. long, 4 to 11 gm. The weight of the spleen ranges up to 15 gm. in fetuses of 48 cm. length; and at 51 cm. length, from 22 to 27 gm. The range of normal variation is so great that the weight of these organs, the thymus and spleen, may not safely be used as an index.

Among the fifty-nine fetuses examined, Schridde found three in which the thymus seemed to him abnormally large. At 54 to 55 cm. fetal length, the thymus weighed 19, 24 and 26 gm., respectively. There was marked hyperplasia of the lymphoid tissue, and the lymph-nodes in the spleen and intestines were visible.

Wernstedt[61] thinks that in nurslings, at least, thymuses of 20 to 30 gm. weight are to be regarded as normal. In fourteen infants who died suddenly in good nutritional condition, the thymus weighed 21.6 to 57.1 gm.

LIPODYSTROPHIA PROGRESSIVA

Feer[62] reports two cases of this little known condition. It is characterized by the occurrence of more or less symmetrically distributed and progressive atrophy of the subcutaneous fat of the patient. Earlier reports on the subject are those of A. Simons[63] and Husler.[64]

Feer's patients were 9½- and 10-year-old girls. His report is accompanied by a study, by one of his pupils,[65] of the normal thickness of the subcutaneous tissue in healthy and ill children.

The Severn.

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[61] Wernstedt, W.: Die Infantile Larynstridor (Stridor congenitus), Nord. Med. Arch., a. f. d. 11, Parts 1 to 4, No. 22; Abstr. in Monatschr. f. Kinderh. (Referate), 1915, **14**, 397.

[62] Feer: Lipodystrophia progressiva, Jahrb. f. Kinderh., 1915, **82**, 1.

[63] Simons, A.: Eine seltene Trophoneurose (Lipodystrophia progressiva), Ztschr. f. d. ges. Neurol u. Psychol., Orig., 5, 1911, **19**, 1913.

[64] Husler, J.: Ueber symmetrischen progressiven Fettschwund im Kindesalter, Ztschr. f. Kinderh., 1914, **10**.

[65] Batkin, S.: Die Dicke des Fettpolsters bei gesunden und kranken Kindern, Jahrb. f. Kinderh., 1915, **28**, 103.

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ERRATA

In the article by Dr. Alfred F. Hess on "Infantile Scurvy" in the January number, page 99, line 9, the specific gravity should be 1.4 instead of 1.04. Page 109, line 15, read "16 ounces," not "sixteen months."

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ACIDOSIS IN CHILDREN, WITH REFERENCE TO THE PATHOLOGIC ANATOMY *

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In the last decade pediatricians have come to recognize a form of acid intoxication occurring in children as a distinct clinical entity, the so-called acidosis.

This type is described by Abt[1] as occurring in robust children who have been previously healthy. Following a period in which the child's weight remains stationary and in which dissatisfaction with the food is shown, the disease becomes manifested by diarrhea, vomiting and a febrile reaction lasting a few days, after which there occur abdominal distention, and pronounced dyspnea characterized by rapid, labored respiration of wide amplitude; the liver becomes palpable, with firm round edges, the urine contains albumin, casts and the acetone bodies; in a few days the child passes into coma which is apt to terminate fatally. On postmortem examination the liver and kidneys are found to have undergone fatty changes. Abt also enumerates a variety of clinical conditions in which the acetone bodies are found, but in which diseases their occurrence is regarded merely as a symptom of the disease. In acidosis, the striking feature is the rapid abrupt clinical course in children who previously have been healthy. Parke[2] states that in several of his patients criminal poisoning was suspected, as in the case to be described.

This paper is concerned with the record of the clinical course and necropsy in a case which we believe to be one of acidosis, and an attempt to correlate the anatomic alterations with the clinical diagnosis.

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[1] Abt: Am. Jour. Med. Sc., 1914, **147,** 86.

[2] Parke: Jour. Am. Med. Assn., 1907, **49,** 1827.

REPORT OF CASE

History.—The patient, a male child aged 16 months, was brought to the Sarah Morris Hospital for Children, Aug. 3, 1915, because of vomiting. The history was that of a normal, robust child, who had been born spontaneously after a normal pregnancy, sat up at 5 months, cut his first tooth at 13 months and began to walk at 14 months; he was breast fed and was apparently in normal condition up to two weeks previous to his entry to the hospital, when he vomited after feeding. Because of this the mother started to wean him, substituting skimmed milk and a proprietary food, but the vomiting continued. The vomitus was dark-brown in color, of thick consistence, but contained no curds or blood. The urine decreased in amount, became dark-brown in color and had an offensive odor. August 1, the mother noticed that the ankles were swollen.

Examination and Course.—On admittance the child was in a drowsy, somnolent state and would shriek at times. The fontanels were closed, there was no tenderness about the head, the face was edematous; the ears were normal; there was strabismus of the right eye, and the pupils reacted to light; the nose was normal; the upper and lower incisors were present; the tongue was coated. The chest was symmetrical, expansion good, resonance normal; the breath sounds were vesicular and a few moist râles were heard posteriorly over both apices. The heart boundaries were normal, the sounds were clear and distinct; the abdomen was distended, the liver was palpable, the extremities were markedly edematous. The temperature was 100 F., the respirations 36 and the pulse 160. Shortly after admittance the child was placed in a mustard pack, stimulants were given hypodermically, and cathartics and alkalies by mouth. In the afternoon the temperature was 104.4 F., the pulse 154, respirations 46. Two-thirds milk with dextromaltose was given, which the child vomited. The following day the child's condition was worse; he refused food, moaned and screamed as if in pain, and only a small amount of urine was passed. The treatment of the previous day was repeated. The respirations became labored and gasping, the temperature, pulse and respiratory rate remained much the same, and he became comatose. The urine was cloudy, dark-amber in color, acid in reaction, contained albumin, acetone and fatty casts, also erythrocytes, leukocytes and fat globules. The blood showed 80 per cent. hemoglobin, 4,200,000 erythrocytes per cubic millimeter, and 10,200 white cells; the differential cell count was normal. The child died forty hours after admittance.

Necropsy.—Anatomic Diagnosis: Lipemia; lipuria; anasarca; marked fatty changes in the liver; marked fatty degeneration of the kidneys; cloudy swelling of the myocardium; passive congestion of the lungs; small accessory spleen.

The body was that of a white, well-nourished male infant weighing 19 pounds 13 ounces. There was present a general anasarca. The tissues of the limbs, body and head were edematous and pitted on pressure. Rigor mortis, algor mortis, and postmortem lividity were present. The hair on the head was 2 cm. in length and light-brown in color; the forehead was prominent, the cheeks puffy and edematous; the eyeballs appeared sunken; the corneas were turbid, the pupils dilated, and the conjunctivas anemic. The fontanels were closed; the tongue was coated. There were three incisor teeth in the upper jaw and two in the lower. The chest appeared normally symmetrical; the costochondral junctions were not enlarged. The abdomen was distended, the liver was palpable, and the testes were in the scrotal sac.

The subcutaneous adipose tissue was marked. The peritoneum was smooth, glistening and of the usual transparency; the intestines were moderately distended; the peritoneal fluid was slightly increased in amount. The appendix appeared normal and lay free in the peritoneal cavity.

The heart lay free in the pericardial sac, which contained about 5 c.c. clear serous fluid. In removing the heart, the fluid blood which escaped contained multiple minute droplets of fat, easily seen in the reflected light. The heart was about the size of the child's fist. The left ventricle was firmly contracted, the right was relaxed; the heart weighed 40 gm. The valves of the heart appeared normal; the myocardium was pale, anemic, and the edge of the freshly cut surface everted.

The lungs lay free in the pleural cavities surrounded by the usual amount of clear serous fluid. The left lung was normal in size, mottled, grayish-red in color; the consistency was normal, and there were present no areas of consolidation. On section, dark, fluid blood escaped from the surface. The lung weighed 50 gm. The right lung was normal in size, weighed 80 gm., floated in water; the consistency was slightly increased, the color mottled grayish-red, and on section dark fluid blood escaped.

The thymus was present in its usual place and measured 2 by 5 cm. It appeared normal.

The liver was enlarged. It extended 3 cm. below the costal arch; the consistence was markedly increased; the superior surface showed indentations of the ribs; the color was bright yellow, that of adipose tissue; it weighed 520 gm. On section, the surface was also bright yellow; it felt fatty; the knife used to cut it was streaked; the parenchyma was swelled, and the cut edge everted.

The spleen was normal in size, the color purplish-red; the consistency was normal; the weight was 15 gm.; on section it appeared normal. There was a small accessory spleen 0.5 cm. in diameter in the gastrocolic ligament.

The left kidney was normal in size and weighed 30 gm.; it was of increased consistency; the color was pale yellowish-red. On section the surface of the cortex was bright yellow, about that of adipose tissue; it felt fatty and streaked the cutting knife; the medulla was bright red. The right kidney presented the same alterations.

The bladder contained 25 c.c. turbid, yellowish urine. The mucosa was pale and anemic. The stomach and intestines appeared normal, and there were present no alterations in the gastric, esophageal or intestinal mucosa.

Microscopic Examination.—In a frozen section of the liver stained with sudan III and hematoxylin there was marked fatty infiltration involving the entire lobule. Regarding the area of the microscopic field as 100 per cent., the morphologic demonstrable fat covers from 70 to 90 per cent of the surface. The only parts free from fat were the blood vessels, the liver capsule, the hepatic canals and the interlobular connective tissue. The liver cells were distended, the nuclei crowded to the sides of the cells; the fat was present as large, discrete globules, 7 to 15 microns, lying within the cells, either single or multiple; the fat globules were highly refractile.

In a section of the kidney similarly prepared, there was present a marked degree of fatty degeneration of the tubules; the glomerules were normal. In a section of the cortex, about three-fourths of the microscopic field was covered by fat, which was present as multiple, fine granules, 1 to 3 microns, of a low refractile index, closely crowded together, occupying the entire cell body of the tubular epithelium. The cells were not increased in size; the nuclei occupied their usual places. The glomerules appeared to have undergone no changes.

In the myocardium there was no evidence of fatty changes. The cytoplasm of the cells appeared granular; the striae were absent; occasional vacuoles were seen. In a section of the lung there were no alterations. Sections of the pancreas, thymus and spleen were normal.

Urine: Twenty-five cubic centimeters of yellowish, turbid urine were obtained from the bladder. It was permitted to remain in a tall glass cylinder in the ice box for several hours, when it separated into a heavy sediment and an opaque supernatant fluid. On microscopic examination of the sediment there were present numerous erythrocytes, epithelial cells, many casts, crystals of ammonium urate and amorphous material. When a drop of sudan III was added to the sediment, the casts were seen to contain numerous fine, fatty globules of a high refractile index, and within the epithelial cells fine fat granules were also present; free fat was also present in the urine. Examined chemically, sugar, albumin, acetone, and diacetic acid were present.

Blood: Blood removed from the great vessels was similarly placed in a tall glass cylinder. It separated into a supernatant yellowish, milky fluid over a dark red coagulum. On the surface of the fluid there was present a stratum of fat. The fat readily stained with sudan III and was of a high refractile index.

Bacteriology: The following fluids were examined: pleural, pericardial, peritoneal, and heart's blood. In direct smears no organisms were found. Suitable culture mediums were inoculated with each fluid and incubated. No growths were obtained.

Because of the suspicions expressed by one of the parents, a portion of the liver was analyzed chemically for phosphorus, according to the method outlined by Autenrieth.[3] No evidence of phosphorus was found; there was no erosion of any part of the intestine. The bacteriologic examination of the several fluids mentioned was carefully performed, the fluids being removed at the time of the necropsy under strict aseptic precautions, and were inoculated within a few hours into suitable culture mediums and were prepared aerobically and anaerobically; also by the newer bacteriologic methods suggested by Rosenow,[4] including the glucose ascites agar mediums for growing organisms under various degrees of "oxygen tension." All the mediums remained sterile after ten days and were discarded. We concluded that we were not dealing with an infection. We then turned for an interpretation of the disease to the anatomic pathology. Reviewing the necropsy, five significant anatomic alterations were found: lipemia, lipuria, fatty infiltration of the liver, fatty degeneration of the kidneys, anasarca.

Lipemia, or an increase of the fat in the blood, occurs in relatively few pathologic states. It has been found in fat embolism associated with fractures (Scriba[5]); in alcoholism by Gumprecht;[6] in metabolic disturbances by Fischer,[7] who found an increase of over one hundred times the normal fat content in diabetes, and in acidosis by Adler.[8] In fat embolism there is a history of trauma and evidence of the injury; in our patient there was neither. Lipemia in alcoholism, reported by numerous authors, is emphatically denied by Quensel.[9] Further, this cause is ruled out in an infant. Lipemia in a metabolic disturbance has to be considered.

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[3] Autenrieth: Detection of Poisons, 1909, p. 4.

[4] Rosenow: Jour. Am. Med. Assn., 1914, **63,** 903.

[5] Scriba: Deutsch. Ztschr. f. Chir., 1880, **12,** 118.

[6] Gumprecht: Deutsch. med. Wchnschr., 1894, **31,** 756.

[7] Fischer: Virchows Arch. f. path. Anat., 1903, **170,** 30.

[8] Adler: Berl. klin. Wchnschr., 1910, **47,** 1323.

[9] Quensel: Alkoholfrågen från Medicinisk Synpunct, Stockholm, 1913, **1,** 144.

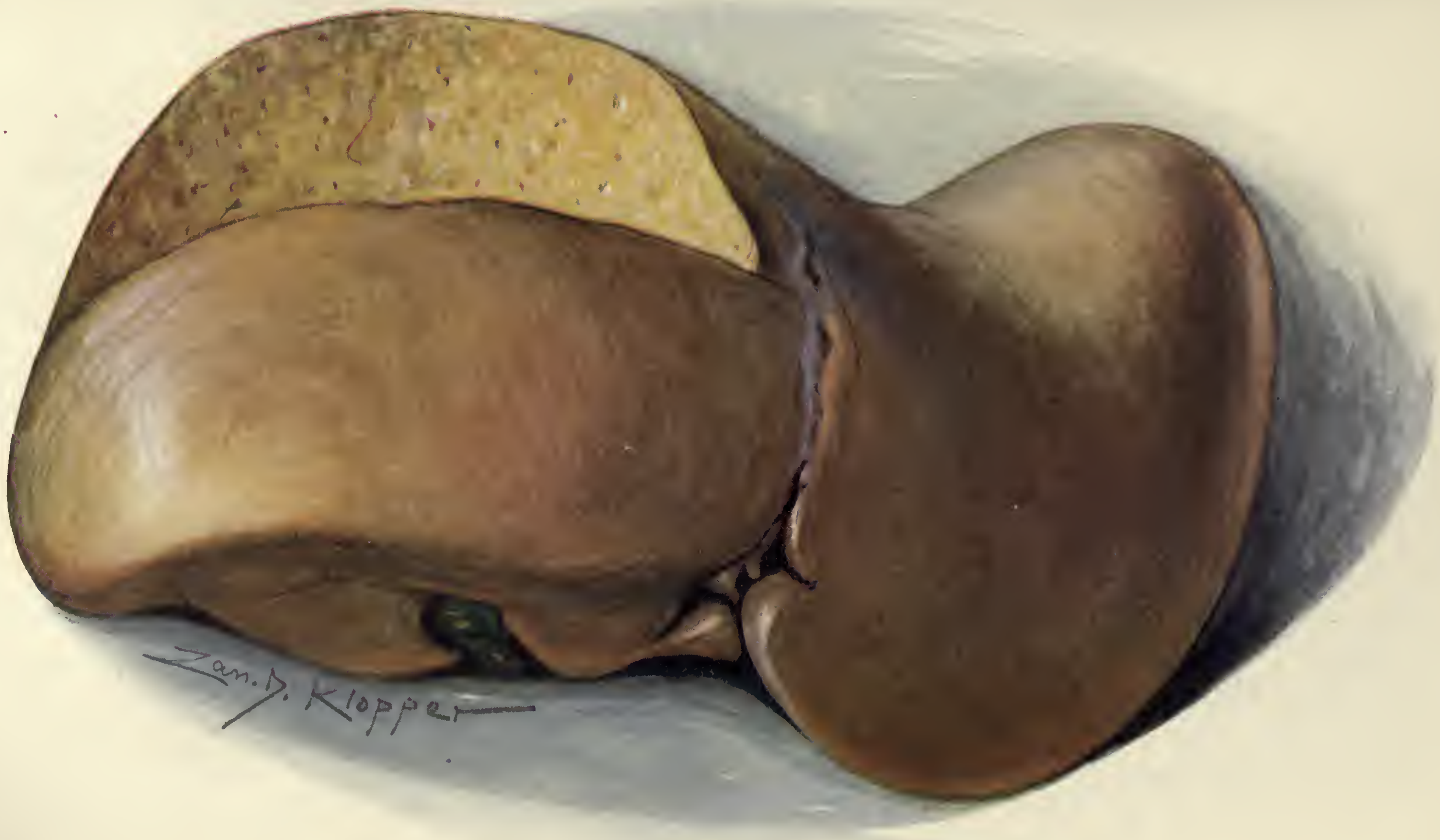

Fig. 1.—Colored drawing of the liver, superior surface. The extreme fatty infiltration is evident from the yellowish color, rounded edges and firm consistency.

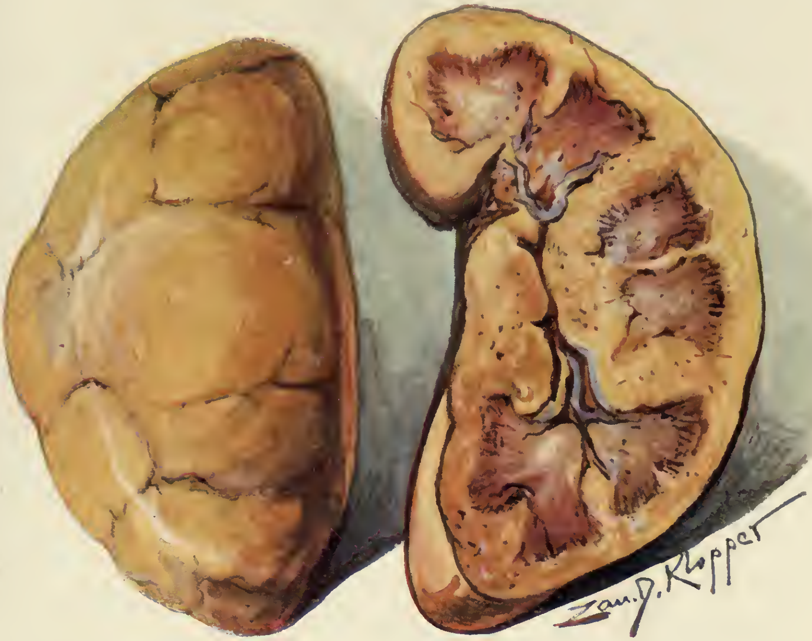

Fig. 2.—Colored drawing of the kidney. Fatty changes are evident from the yellowish, firm outer surface, and the yellowish, swollen cortex of the cut surface and absence of cortical radiations.

Lipuria is usually associated with lipemia, occurring as an outward expression of the increased fat content of the blood, when some of the blood fat is excreted by the kidney into the urine; further, lipemia is apt to occur in those conditions which produce fatty changes in the kidneys, when fat is thrown into the urine as free globules or as fatty casts, from which the fat globules may become loosened as a result of the breaking down of the tubules. In this instance both conditions were present to account for the lipuria; that is, lipemia and fatty kidneys.

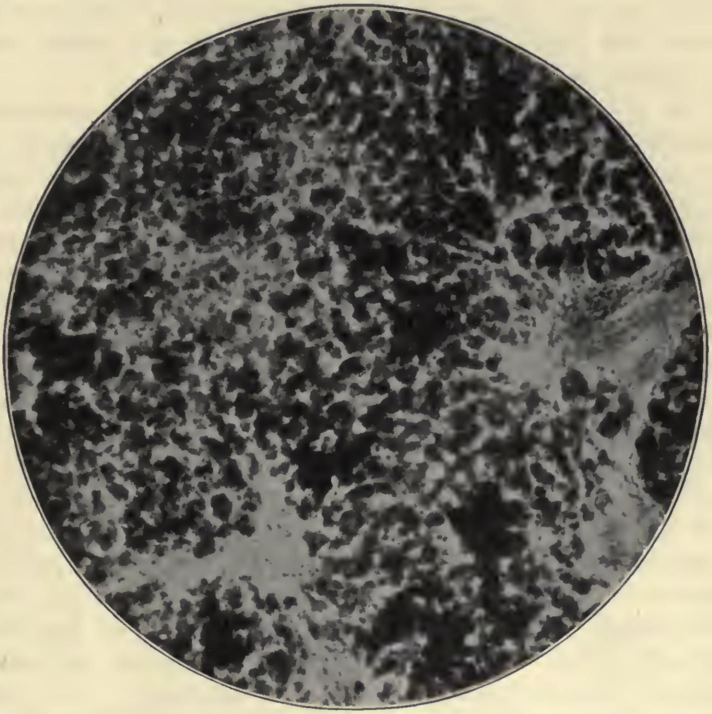

Fig. 3.—Photomicrograph of a frozen section of the liver stained with sudan III and hematoxylin, illustrating the extreme fatty infiltration. All of the dark-staining substance except the blood vessels, connective tissue, and parenchyma cell nuclei, is fat.

In normal liver tissue, employing the ordinary fat stains, little or no fat can be seen microscopically. Fatty infiltration, a condition in which morphologically demonstrable fat occurs, is present in a large variety of conditions. Helly,[10] who studied fatty infiltration in numerous pathologic states, found the fat content of the liver to vary from 7 to 74 per cent., the higher values occurring in conditions associated with metabolic disturbances. Mottram[11] enumerates the diseased states of the body that are accompanied by fat infiltration of the liver; also those conditions in which the acetone bodies are found increased in the blood and urine. He states that the two series are practically identical. In 1847 Virchow divided the forms of fatty changes of the liver into infiltration and degeneration. These terms have persisted, but they are now regarded as denoting two anatomic types of one alteration. All increased fat of the liver is infiltrated. The liver acts as a fat depot, and the fat in the depot is of the nature and character of the fat given in the food. The fat is present in the liver for physiologic and not pathologic reasons. These general conclusions are asserted by Wells,[12] Mottram[11] and others, and are based on the work of Lebedeff, Rosenfeld and other writers, whom the authors named, cite.

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[10] Helly: Verhandl. deutsch. path. Gesellsch., 1914, **17**, 136.

[11] Mottram: Canad. Med. Assn. Jour., 1915, **5**, 603.

In the normal kidney, also, little or no fat can be demonstrated microscopically, although the fat content (lipins) of the kidney is about 18 per cent. of the dry weight, whereas a pathologic kidney containing but 16 per cent. fat (lipins) of its dry weight may show extreme fatty degeneration. (Wells,[12] p. 365.) An increase in the microscopic demonstrable fat when ordinary fat stains are employed, does not denote an increase in the fat content and is interpreted as fatty degeneration, whereas in the liver an increase is regarded as infiltration. In the kidney of our patient there was a marked fatty degeneration of the tubules, while the glomerules appeared normal. Howell[13] states that the glomerules excrete water and the simple salts, while the tubules excrete substances of a larger chemical molecule, including sugar, urea, albumin, toxins, etc. If the acetone bodies in the blood are excreted into the urine and they are capable of producing fatty degeneration, one would expect to find the fatty changes in the tubules and in the tubules only. Recently Pearce and Brown[14] have produced, experimently, changes in the kidneys of dogs by intravenous injection of arsacetin, in which "the cortex is widened, the striations are yellowish opaque and raised as a result of the tubular necrosis; . . . microscopically, the glomerules are normal, and practically all of the epithelium of the convoluted tubules is necrotic."

The exact mechanism of disease production in acidosis is not clearly understood. Numerous writers have pointed out that it has not been established whether the acidosis is the cause, result, or a concomitant symptom of the disease in which it occurs. In this discussion thus far we have assumed the lipemia as a starting point to explain the pathologic changes. We now hope to point out the relation between the lipemia and acidosis.

Howell teaches that in the normal process of digestion, fat, after its emulsification in the intestinal tract, is absorbed by the lacteals of the intestine and is carried by the lymphatics to the thoracic duct which carries it into the blood stream. After each meal there occurs a temporary physiologic increase in the fat content of the blood. Any condition which causes an impairment of the mechanism of removal of the fat from the blood might account for pathologic lipemia. Normally, fat is removed from the blood in three ways: first, it is carried to the fat depots, as the liver, omentum, etc., to be stored; second, it is carried to the tissues of the body, where it is oxidized to supply body heat; third, it is synthesized to form more complex substances, as lecithin.

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[12] Wells: Chemical Pathology, 1914, p. 361.
[13] Howell: Textbook of Physiology, 1910, p. 802.
[14] Pearce and Brown: Jour. Exper. Med., 1915, **22,** 517.

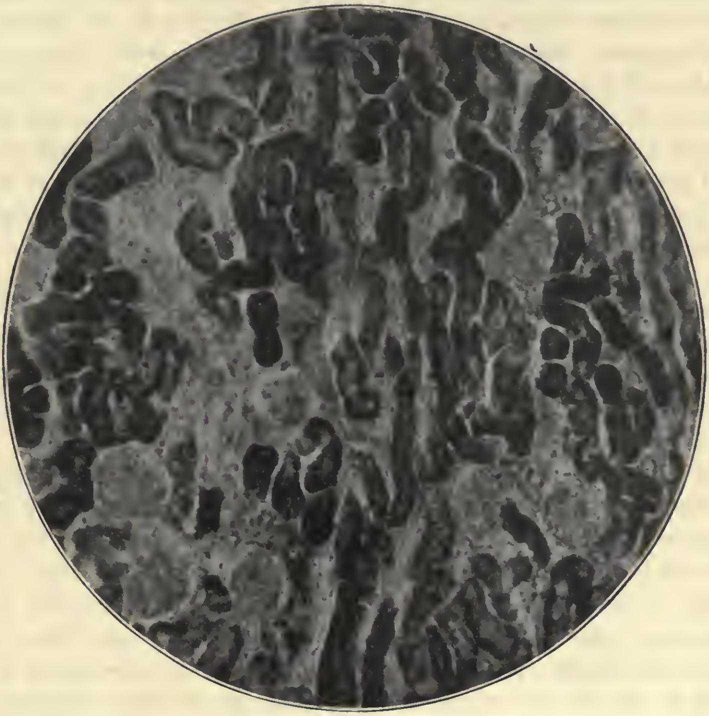

Fig. 4.—Photomicrograph of a frozen section of the kidney cortex stained with sudan III and hematoxylin. All of the tubules have undergone fatty degeneration, the glomerules are normal.

In the blood of acidosis there occurs a perceptible increase in acetone, beta-oxybutyric acid and diacetic acid. Marriott[15] has shown that the blood of normal human subjects contains less than 1.5 mg. aceto-acetic acid, and less than 4 mg. beta-oxybutyric acid per 100 gm. blood, the results being expressed in terms of acetone, while in acidosis there is a marked increase. The highest figure he obtained was in acidosis of diabetes, in which there was 28 mg. aceto-acetic acid and 45 mg. oxybutyric acid per 100 gm. of blood expressed as acetone.

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[15] Marriott: Jour. Biol. Chem., 1914, **18,** 507.

This excess of acid bodies in the blood is held in neutral state by combination with the alkalies of the blood. In acidosis the "alkali reserve" is thereby diminished. Recent writers have published various observations on the alterations of the hydrogen-ion concentration of the blood in acidosis in which they demonstrate a shifting of the reaction of the blood in the direction of acidity; but at no time can this alteration be marked. Henderson[16] has shown that not more than five parts of excess free H or OH ions can be present in ten billion parts of protoplasm. Wells[17] asserts that acidity is impossible, because death would result from the inability of the blood to carry CO_2, and likewise alkalinity is impossible, because this would cause an increased osmotic pressure which the kidneys would regulate. The acetone bodies in the blood hold in combination molecular proportionate amounts of alkalies which are thereby removed from the function of performing internal respiration; that is, carrying CO_2 to and from the body tissues. With diminished CO_2 carrying power of the blood, the body attempts to compensate by increasing the amplitude and rate of the respiratory movements (Czerny,[18] Henderson[19]); the CO_2 pressure of the alveolar air, nevertheless, falls (Kennaway, Pembrey and Poulton,[20] Howland and Marriott[21]); and because of the lessened oxidation in the lungs, CO_2 is retained in the tissues and internal asphyxia follows. With impairment of oxygenation, the metabolism of fats together with other processes involved in oxidation, become imperfect. This may explain a retardation of the tissues in utilizing the fats of the blood for oxidation and heat production, resulting in fat retention by the blood — lipemia. Further, with imperfect metabolism of the fats, the acetone bodies are formed as intermediate products. It is obvious that a vicious circle soon becomes established, for the greater the amount of acetone bodies in the blood, the more the respiration becomes impaired; and the more respiration is impaired, the greater becomes the production of the acetone bodies; which may explain the rapid course of the disease so frequently observed.

Further, if we follow the principles of Fischer's theory of edema, that the hydration capacity of asphyxiated tissue is tremendously increased, the general edema observed in this instance is explained by the internal asphyxia resulting from the impaired respiration in the lungs and diminished CO_2 carrying power of the blood.

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[16] Henderson: Am. Jour. Physiol., 1907, **18,** 250; ibid., 1908, **21,** 427.

[17] Wells: Chemical Pathology, 1914, p. 263.

[18] Czerny: Jahrb. f. Kinderh., 1897, **45,** 271.

[19] Henderson: Jour. Am. Med. Assn., 1914, **63,** 318.

[20] Kennaway, Pembrey and Poulton: Jour. physiol., 1913, **48,** 10.

[21] Howland and Marriott: AM. JOUR. DIS. CHILD., 1916, **11,** 309.

CONCLUSION

There occurs in acidosis, lipemia from the failure of the body tissues to utilize the fats in the blood.

Lipuria, an outward expression of lipemia, also resulting from the excretion of fat in the waste products of the kidneys as fatty casts.

Fatty infiltration of the liver, which is a physiologic accumulation of fat from the blood.

Fatty degeneration of the kidneys resulting from acid intoxication.

Anasarca resulting from impaired internal and external respiration.

THE OCCURRENCE OF ACIDOSIS WITH SEVERE DIARRHEA *

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INTRODUCTION

The toxic symptoms which may occur in infants suffering from severe diarrhea are striking and characteristic. Prominent features are the evidence of fluid loss (sunken eyes, depressed fontanel and inelastic skin), a mental state which is usually dull and apathetic, often terminating in stupor, but at times characterized by periods of excitement, and increased pulmonary ventilation. The urine of infants thus affected almost regularly contains a reducing substance.[1]

Recently Howland and Marriott[2] have shown that in many cases of this type, especially those showing hyperpnea, there is evidence of acidosis. This evidence was as follows: (1) decreased tension of carbon dioxid in the alveolar air; (2) Sellard's test for the reaction of blood serum; (3) altered hemoglobin dissociation curve; (4) increased tolerance to sodium bicarbonate; (5) increased hydrogen-ion concentration of the blood.

During the past three years we have accumulated data which have a bearing on this subject and which we propose to present at this time. Investigations were made on more than 200 infants. These consisted in the determination of the carbon dioxid in the blood, the carbon dioxid in the alveolar air, the carbon dioxid combining power of blood

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[1] To save space and to avoid needless repetition the presence of these symptoms will be designated by the terms "toxic symptoms" or "intoxication." These terms are not used to designate the complex described by Finkelstein as "Alimentary Intoxication." They are used merely to differentiate the cases of diarrhea without general symptoms from those which show the severe disturbances which frequently occur in the course of this disease.

In twenty cases one of us (O. M. S.) has been able to obtain a sufficient amount of urine to determine with a fair degree of accuracy the nature of the reducing substance. Despite the accepted views of Langstein and Steinitz, von Reuss and others, that this substance is lactose or galactose, our results indicate that dextrose alone, or dextrose in combination with galactose or lactose, is usually present. The details will be the subject of a later communication.

[2] Howland, J., and Marriott, W. McK.: Acidosis Occurring with Diarrhea, AM. JOUR. DIS. CHILD., 1916, **11,** 309.

plasma, the tolerance to sodium bicarbonate, the presence of acetone bodies in the urine and the ammonia coefficient of the urine.

I. THE CARBON DIOXID OF THE BLOOD OR ALVEOLAR AIR AND THE CARBON DIOXID COMBINING POWER OF BLOOD PLASMA

1. *The Carbon Dioxid Content of the Blood.*—The determinations were made by the method of Barcroft and Haldane.[3] Blood was collected over mercury in modified Brodie pipets and herudin was used to prevent coagulation. In most instances the determinations were made in duplicate, and always when the values were low.

In twenty infants not acutely ill and free from digestive disorders the values ranged from 36 to 46 volumes per cent.[4] In infants affected with severe diarrhea accompanied by toxic symptoms, the carbon dioxid was much reduced (Table 1).

TABLE 1.—Carbon Dioxid in Blood in Severe Diarrhea with Toxic Symptoms

Case	CO_2, Volume per Cent.	Case	CO_2, Volume per Cent.	Case	CO_2, Volume per Cent.
1	26	10	16	19	26 22
2	18	11	24 20	20	30 27
3	19	12	19	21	29 19
4	21 23	13	25	22	26
5	19 18	14	23 21	23	23
6	17 21	15	24	24	28 23
7	19	16	21 17	25	24
8	22	17	24 21	26	27
9	27 19	18	19		

2. *The Carbon Dioxid Combining Power of Blood Plasma (Van Slyke).*—The estimations were made according to the technic of Van Slyke.[5] Blood was collected, with sufficient potassium oxalate to make a concentration of about 1 per cent., centrifugalized immediately, and when the determination could not be made at once, the plasma was kept on ice in paraffined bottles until used. In most instances the

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[3] Barcroft, J., and Haldane, J. L.: A Method for Determining Oxygen and Carbon Dioxid in Small Amounts of Blood, Jour. Physiol., 1902, **28,** 232.

[4] These figures represent venous blood and are accordingly higher than those which would hold for arterial blood or alveolar air.

[5] Van Slyke, D. R.: Proc. Soc. Exper. Biol. and Med., 1915, **12,** 165.

determinations were made within twenty-four hours. The cases may be separated into four groups.

a. Infants not Acutely Ill and with no Digestive Disorder.—The values ranged from 46.2 to 76.1 volumes per cent. of carbon dioxid (Table 2). The fact that infants may show lower values than adults has been noted by Van Slyke. Our determinations did not show uniformly low values, but rather a wide variation, with a tendency to be lower than in adults. In a number of cases the figures were the same as for normal adults.

TABLE 2.—Carbon Dioxid Combining Power of Blood Plasma (Van Slyke) in Normal Infants *

Number	Age	Weight, Pounds	CO_2, Volume per Cent.	Number	Age	Weight, Pounds	CO_2, Volume per Cent.
1	3 weeks	7	58.6	15	6 months	13¾	47.1
2	4 weeks	6½	49.0	16	7 months	13	53.8
3	4 weeks	8	54.8	17	8 months	15½	56.7
4	5 weeks	8½	46.2	18	8 months	14¾	50.0
5	6 weeks	9	52.8	19	8 months	15	51.0
6	6 weeks	8¾	75.8	20	9 months	13½	46.2
7	8 weeks	10	59.5	21	11 months	14½	54.8
8	9 weeks	10½	55.7	22	12 months	19½	51.9
9	3 months	10	54.8	23	13 months	21¾	60.5
10	3½ months	10½	56.7	24	13 months	19	61.4
11	3½ months	9¾	48.1	25	16 months	18¾	51.0
12	4 months	12	55.7	26	17 months	24	61.4
13	4 months	11½	53.8	27	18 months	22	63.3
14	6 months	14	49.0				

* These infants were normal in the sense that they were suffering from no acute illness or digestive disorder. They all, however, were under weight.

Although we attempted to take the blood for examination about one-half hour before feeding (from two and a half to three and a half hours after feeding), this time often varied, and it seemed of interest to determine whether digestion had an influence in causing the low results. Accordingly, we made determinations directly before and directly after feeding in six infants, and in another series, directly before and one hour after feeding (Table 3). These observations, while they show a rise in carbon dioxid after feeding,[6] give no explanation for the low values at times found in normal infants. We also tabulated the cases on the basis of the variety of food and method of feeding but found no constant relationship between either and the carbon dioxid values.

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[6] That such a rise occurs is well known and has been demonstrated by the following observers: Porges, Leimdorfer, and Markovici: Ztschr. f. klin. Med., 1911, **73,** 389; Hasselbach: Biochem. Ztschr., 1912, **46,** 403; Higgins: Am. Jour. Physiol., 1914, **34,** 114.

In the absence of a definite explanation we can only state that in apparently normal infants the carbon dioxid combining power of blood plasma varies within rather wide limits. It seems possible, as Marriott suggests, that the low carbon dioxid values at times obtained in infants result from their more active metabolism, leading to a disproportionately greater production of acids.

b. Cases of Minor Nutritional Disorders.—In this group were twenty infants who were not acutely ill, but who were gaining slowly or not at all, and presented mild digestive symptoms such as occasional vomiting and stools which were of abnormal character or frequency. The carbon dioxid ranged from 48.1 to 67.2 volumes per cent. and was therefore within the limits of normal.

TABLE 3.—The Influence of the Ingestion of Food on the Carbon Dioxid Combining Power of Blood Plasma

Number	CO_2, Volume per Cent.		Number	CO_2, Volume per Cent.	
	Directly Before Feeding	Directly After Feeding		Directly Before Feeding	One Hour After Feeding
1	52.8	56.8	1	47.1	49.0
2	60.5	67.6	2	53.8	54.9
3	62.4	64.3	3	53.8	54.8
4	50.0	52.8	4	59.5	60.5
5	55.7	57.6	5	62.0	69.5
6	54.8	56.8	6	62.0	63.8

c. Cases of Diarrhea.—These infants were suffering from moderate or severe diarrhea, but at the time the examination was made did not present definite toxic symptoms. This group is of special interest, as most cases of intoxication are preceded by diarrhea[7] (Table 4). In a number of instances the carbon dioxid was decreased in the absence of severe general symptoms, and served as a warning of developing intoxication. It is of interest also that there was no pronounced increase in the frequency or depth of the respirations. Of further interest is the fact that in three cases (5, 9, 17) the diarrhea terminated fatally, and there was no reduction in the carbon dioxid.

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[7] Although this is usually true, yet cases occur which present the typical symptoms of intoxication without diarrhea. There were four cases in this series with the toxic symptoms often associated with diarrhea, but with no history of diarrhea and none during observation.

d. Cases of Intoxication.—There were twenty cases of intoxication, and in eighteen the carbon dioxid combining power of the blood plasma was greatly reduced (Table 5). In Cases 6 and 13 hyperpnea was not observed, but with this exception the symptoms were distinct. In both cases there was no decrease in the carbon dioxid combining power of the blood plasma. The estimations were made in duplicate and on two separate occasions.

TABLE 4.—Carbon Dioxid Combining Power of Blood Plasma in Infants with Diarrhea But Showing No Toxic Symptons

Number	Age, Months	CO_2, Volume per Cent.	Remarks
1	4	33.5	Developed intoxication*
2	4	58.4	Recovered
3	5	57.6	Recovered
4	5	32.8	Developed intoxication*
5	5	55.7 - 58.6 - 56.7	Died; no symptoms of intoxication
6	6	42.4	Developed intoxication*
7	6	51.0	Recovered
8	6	46.2	Recovered
9	6	48.1 - 51.0 - 50.0	Died; did not develop intoxication
10	7	45.3	
11	7	59.5	Died†
12	7	60.5	Recovered
13	8	31.9	Developed intoxication*
14	8	30.0	Developed intoxication*
15	9	55.7	Recovered
16	9	54.8	Recovered
17	9	55.7	Died†
18	10	32.8	Developed intoxication*
19	10	30.0	Developed intoxication*
20	11	53.8	Recovered
21	11	57.6	Died†
22	11	51.9	Recovered
23	12	52.8	Recovered
24	12	42.4	Developed intoxication*
25	13	49.0	Recovered
26	13	51.0	Recovered
27	13	54.8	Recovered
28	14	55.7	Recovered

* The symptoms of intoxication developed within two days after this determination was made.

† In Cases 11, 17 and 21 no further carbon dioxid determinations were made. In all three cases, however, death occurred within forty-eight hours and the infants were very ill at the time of observation.

3. *Carbon Dioxid Content of Alveolar Air.*—By a method of air collection similar to that used by Howland and Marriott[8] the alveolar air was analyzed in the Haldane apparatus. Such analyses were made on expired air from normal infants, infants suffering from simple diarrhea and infants with intoxication. The results were practically identical with those obtained by Howland and Marriott and those obtained by us with other methods. It is therefore unnecessary to cite these results in detail, but some of them will be referred to later.

TABLE 5.—Carbon Dioxid Combining Power of Blood Plasma in Infants with Intoxication *

Number	Age, Months	CO_2, Volume per Cent.	Number	Age, Months	CO_2, Volume per Cent.
1	2	20.4	11	7	18.5
2	3	17.6	12	7	24.2
3	3	21.4	13	8	56.7 54.8
4	4	26.2	14	8	27.1
5	4	23.3	15	8	30.9
6	5	51.9 52.8	16	9	25.2
7	6	12.8	17	9	18.5
8	7	26.2	18	11	25.2
9	7	27.1	19	11	37.6
10	7	19.5			

* In a number of these cases several determinations were made, but only the lowest values are given in the table.

DISCUSSION OF RESULTS OF CARBON DIOXID DETERMINATIONS

It is unnecessary to consider in detail the significance of the carbon dioxid content of the blood or expired air, as this subject and the literature have been discussed by Peabody,[9] Higgins and Means,[10] Howland and Marriott,[11] Marriott[12] and others. It seems definitely established that with the exception of unusual conditions such as diminished excitability of the respiratory center or altered permeability of the respiratory epithelium, a reduction of the carbon dioxid of the blood signifies a diminution of the fixed alkali of the blood and therefore a condition of acidosis.

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8. This method is an adaptation to infants of the Plesch-Higgins method. Plesch: Ztschr. f. exper. Path. u. Therap., 1909, **6,** 380; Higgins: Pub. 203, Carnegie Inst., Washington, D. C., 1915, p. 168.

9. Peabody, F. W.: Some Aspects of the Clinical Study of the Respiration: The Significance of Alveolar Air Analysis, Am. Jour. Med. Sc., 1916, **151,** 184.

10. Higgins and Means: Jour. Pharmacol. and Exper. Therap., 1915, **7,** 1.

11. Howland and Marriott: Bull. Johns Hopkins Hosp., 1916, **27,** 63.

12. Marriott: Arch. Int. Med., 1916, **17,** 840.

Our results, therefore, agree with those of Howland and Marriott, that in the intoxication due to diarrhea there is usually a distinct acidosis.

The only clinical sign which is at all characteristic is the increased pulmonary ventilation or hyperpnea. This sign when unaccompanied by cyanosis is almost diagnostic. From physiologic considerations one would expect an increase in the respirations whenever there was a pronounced lowering of the carbon dioxid. This, however, was not true in all of our cases. In 65 patients with a pronounced reduction of the carbon dioxid of the blood or alveolar air, the presence or absence of hyperpnea was noted in 40. It was present to some degree in 31 and absent in 9. These patients, however, were examined only once or twice a day and it seems quite possible that the increased pulmonary ventilation may be intermittent and might thus be overlooked. That these patients were actually suffering from acidosis is borne out by the fact that in 5 the carbon dioxid became normal after the administration of sodium bicarbonate.

II. TOLERANCE TO SODIUM BICARBONATE

It has been shown by Sellards[13] and by Palmer and Henderson[14] that the amount of sodium bicarbonate required to render the urine alkaline is fairly constant in normal adults, and that in acidosis the tolerance is much increased.

Our first consideration was the tolerance of infants not affected with acidosis.[15] The administration of the sodium bicarbonate was controlled by a preliminary carbon dioxid determination to exclude the presence of acidosis, and a test of the reaction of the urine to litmus to be sure that it was acid before the bicarbonate was administered.

Infants from 3 to 12 months old required from 1.25 to 3.25 gm. of sodium bicarbonate when given in a single dose by mouth to render the urine alkaline (Table 6). There is no regular and definite correspondence between the amount of sodium bicarbonate required and the age or weight, but as a rule the older, heavier infants required larger amounts; but these amounts were in no way directly proportional to age or weight.

When we came to determine the tolerance of infants with acidosis we found that the administration of large doses of sodium bicarbonate by mouth was an unsatisfactory procedure. Even normal infants frequently vomit, and this was so often true of those with severe diarrhea that the method was abandoned. We were able to determine the tolerance in six cases, and found that it was much increased (Table 7).

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[13] Sellards: Bull. Johns Hopkins Hosp., 1914, **25,** 141.

[14] Palmer and Henderson: Arch. Int. Med., 1913, **12,** 153.

[15] Our conception of the tolerance of normal infants to sodium bicarbonate is the single dose necessary to render the urine alkaline. In cases of acidosis the point of tolerance is indicated by the single dose of sodium bicarbonate necessary to raise the carbon dioxid to normal. In making the determinations we gave gradually increasing amounts (0.2 to 0.6 gm. increase at each dose) of the drug at intervals of five to eight hours until the proper dose was reached.

The subcutaneous method was not used, as the sodium bicarbonate is partly changed to carbonate by heating, and sodium carbonate is very irritating when given subcutaneously. It is possible to change any sodium carbonate thus formed by passing carbon dioxid through the solution (Magnus-Levy), but owing to the ease and safety of intravenous injections the latter method was used.

TABLE 6.—Amount of Sodium Bicarbonate by Mouth Necessary to Render the Urine Alkaline. Normal Infants

Number	Age, Months	Weight, Pounds	Sodium Bicarbonate, Gm.	Number	Age, Months	Weight, Pounds	Sodium Bicarbonate, Gm.
1	3	11	1.75	10	8	16½	2.75
2	4	12	2.0	11	9	16¾	2.75
3	4	11¾	2.25	12	9	17	3.0
4	5	13	2.25	13	10	18	2.50
5	5	13½	2.75	14	11	17½	2.75
6	6	14½	2.25	15	12	20	3.0
7	6	15	2.5	16	12	20	3.0
8	7	15½	2.5	17	12	19½	3.75
9	8	16	2.25	18	12	19	3.25

TABLE 7.—Amount of Sodium Bicarbonate by Mouth Necessary to Render the Urine Alkaline and to Cause Increase of Carbon Dioxid of Blood or Alveolar Air to Normal. Intoxication

Number	Age, Months	Weight, Pounds	CO_2 Before Giving Alkali	CO_2 After Giving Alkali	Sodium Bicarbonate, Gm.
1	4	9	21	48	6.0
2	5	9½	19.6	40	7.0
3	6	10¾	24	49	5.5
4	6	12½	26	52	6.5
5	6	13	23	45	7.0
6	7	14	19	51	6.5

Doses of 1 to 2 gm. of sodium bicarbonate intravenously are sufficient to render alkaline the urine of infants not affected with acidosis. This is not only smaller than the amount required by mouth, but it was noted also that when administered per os it was often one to three hours before the urine became alkaline, while by the intravenous method it required usually only one-half to one and a half hours. The tolerance of fifteen infants with acidosis showed the same results. The effect was more prompt and the dose required was smaller (Table 8).

Our results show, therefore, that in intoxication there is a great increase in the tolerance to sodium bicarbonate. They demonstrate also that the intravenous method gives a prompter result and with a smaller dose.

TABLE 8.—The Amount of Sodium Bicarbonate by Intravenous Injection Necessary to Render the Urine Alkaline and to Increase the Carbon Dioxid of Blood or Alveolar Air to Normal. Intoxication

Number	Age, Months	Weight, Pounds	CO_2 Before Giving Alkali	CO_2 After Giving Alkali	Sodium Bicarbonate, Gm.
1	4	8	25	39	3.5
2	4	8½	21	47	3.0
3	5	9	19	50	3.5
4	5	11	23	43	4.0
5	5	10½	20	54	5.0
6	7	12	22	45	3.5
7	7	13	21	41	4.0
8	7	12	17	47	5.0
9	8	14	19	46	5.5
10	8	11	24	50	5.0
11	8	13	20	48	4.5
12	10	14	18	39	5.5
13	11	13½	26	46	5.5
14	12	14½	22	44	6.0
15	12	16½	20	49	5.5

III. THE AMMONIA COEFFICIENT IN THE URINE

The quantity of ammonia excreted in the urine and its ratio to the total nitrogen varies greatly in small infants and bears relationship to the type of food. Very high values are sometimes obtained in infants with malnutrition or diarrhea in the absence of any noticeable change in the carbon dioxid of the blood or alveolar air. The presence of a high ammonia coefficient cannot therefore be accepted as conclusive evidence of acidosis, at any rate not in the present conception of the term.

We made determinations of the ammonia in 16 cases of intoxication. In 14, the coefficient was above 20. In two instances it was 8 and 12.5, respectively, which are not unusual figures for infants with nutritional disorders.

IV. PRESENCE OF ACETONE AND DIACETIC ACID IN THE URINE

The urine of many infants with intoxication showed a small or moderate amount of acetone and diacetic acid. These substances were not present in amounts proportional to the severity of the symptoms or to the degree that the carbon dioxid was reduced. Indeed, in three of the severest cases of acidosis (carbon dioxid tension of alveolar air 16, 18 and 19, respectively) acetone bodies could not be demonstrated in the urine. Since most of the infants with intoxication were on diets which represented at least partial starvation, the presence of small amounts of acetone bodies in the urine is without significance. Howland and Marriott found no significant increase in the acetone bodies in the blood or urine of their patients.

GENERAL DISCUSSION

The onset of intoxication is usually gradual and follows, in most cases, a sharp attack of diarrhea. In a number of instances we have made determinations of the carbon dioxid in infants suffering with nutritional disorders, and by this means were able to determine the onset of acidosis. The following case serves as an illustration:

Baby F., aged 6 months, weight 13 pounds. For about a week there had been a slight loss of weight and the patient had from three to six slightly loose stools each day. June 10 the carbon dioxid of the venous blood was 40 volumes per cent. The infant became worse, and successive daily determinations showed carbon dioxid of 37, 30, 28, 24, and 15 volumes per cent., respectively. It was only when the carbon dioxid reached 24 that the respirations became noticeably exaggerated and the toxic symptoms became marked.

In some instances the onset of the acidosis is sudden and the carbon dioxid value of one day may be normal and that of the next day show a decided reduction.

Not all cases of severe diarrhea terminate in acidosis, and as Howland and Marriott point out, the disease may end fatally and be accompanied at no time by reduction of the carbon dioxid values. We have seen several well marked cases of intoxication which presented the usual symptoms, with the exception of hyperpnea, and in which there was at no time any reduction in the carbon dioxid and no increase in the tolerance to sodium bicarbonate or improvement after its administration. The following case was of this type:

Baby D., 7 months old, had diarrhea for one week. There were four to fifteen green watery stools a day and occasional vomiting. The fontanel was sunken, there was evidence of great loss of weight, the skin was dry and inelastic. The mental condition was dull, although at times the baby was excited and would emit loud, sharp cries. The respirations were not noticeably increased in rate or depth.

Time	Carbon Dioxid, Venous Blood, Volumes Per Cent.	Carbon Dioxid Tension, Alveolar Air, Mm.	Urine
10 a. m.	41.0	39.0	Acid
11 a. m.	42.2	41.3	

Three grams of sodium bicarbonate were given by intravenous injection.

Time	Carbon Dioxid, Venous Blood, Volumes Per Cent.	Carbon Dioxid Tension, Alveolar Air, Mm.	Urine
12 m.	44.4	42.2	Alkaline
1 p. m.	44.6	43.0	Alkaline

There was no improvement in the symptoms and death occurred at 6 p. m.

Such cases demonstrate that intoxication is not always accompanied by acidosis, and in the absence of hyperpnea the diagnosis must rest on laboratory evidence.

Treatment.—The acidosis is best treated by the administration of sufficient sodium bicarbonate to increase the carbon dioxid to normal or to render the urine alkaline. Provided that the urine is tested fresh, the two tests are of about equal value and in a number of cases we found that almost coincidently the urine became alkaline and the carbon dioxid normal.

According to our experience, the most satisfactory method of administration is by intravenous injection. It is a very difficult matter for these infants to take by mouth and to retain the required amount of alkali, and unless a sufficient quantity be given the treatment is practically useless. We have also tried the administration of sodium bicarbonate by rectal instillation (Murphy drip), but the results were unsatisfactory. The fluid was usually expelled, and in no instance was a sufficient amount absorbed to influence the carbon dioxid values. To give the alkali subcutaneously requires careful preparation of the solution and the injection of a comparatively large amount of fluid in relation to the size of the infant.

The intravenous injection of 75 to 150 c.c. of a 4 to 5 per cent. solution of sodium bicarbonate is usually sufficient for the first treatment.[16] If the dose is adequate the carbon dioxid becomes normal and in many instances above normal, hyperpnea ceases and there is great improvement in the general appearance of the patient. This change is very striking to observe: the face loses its drawn appearance, the patient becomes alert and comfortable and the skin softer and more elastic.

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[16] If a scalp vein of sufficient size is evident this may be used. In most instances, however, it is necessary to expose a vein by incision or to give the injection into the superior longitudinal sinus. (Tobler: Monatsch. f. Kinderh., 1915, **13**, 384; Helmholz: Am. Jour. Dis. Child., 1915, **10**, 194.) The latter seems preferable in every way. The fluid is best given by gravity and should be given slowly. A cylinder with a capacity of 30 to 100 c.c. may be used. One end of a piece of rubber tubing is attached to the cylinder and the other end has a connecting tip which fits into the needle. It is of advantage to have a stopcock either at the end of the cylinder or near the end of the tubing. The needle is inserted with a small syringe attached, and by slight aspiration one can determine whether the sinus has been entered. If so, the syringe is detached and the apparatus for the injection, which has been filled and the air expelled, is connected. A needle ½ inch long, of 20 to 22 gage, and with a short, bevel point, is of advantage in entering the sinus.

Whether the first dose of bicarbonate is sufficient can be determined by the change in the carbon dioxid[17] and the general improvement in the patient. In addition to the intravenous injection it seems advisable to give sodium bicarbonate by mouth in 2 to 5 per cent. solution so that the patient will receive 2 to 5 gm. per diem in this manner. Within eight hours a second intravenous injection should be given if necessary. The necessity for repeated injections has been present in most of our cases, and the best results have been attained in those which were most carefully observed and the sodium bicarbonate repeated as soon as the carbon dioxid is again below normal.

Unless the infant is moribund, improvement frequently occurs, but despite this improvement the patient often succumbs. Death has occurred in 86 per cent. of the cases with which this paper is concerned. These results, however, include the earlier cases, in which the infants were not thoroughly treated, and also a number of infants who survived the acidosis, but died later of malnutrition. The results in our more recent cases have been more satisfactory.[18] In the cases in which the acidosis has been thoroughly treated, the fatal outcome has been due to one of two causes. 1. Recurrence of the acidosis. This has occurred in a few instances and the acidosis has been very acute and quickly fatal. 2. The usual circumstance is that the infant develops malnutrition of a very severe grade and despite all resources of feeding, gradually wastes away. It would seem that there is some profound disorder of metabolism of which the acidosis merely is a symptom.

There remains one point for further discussion, namely, the dietetic treatment. At present little that is definite and positive can be said, and a successful dietetic therapy can be achieved only by a thorough understanding of the basic nutritional fault. We have usually given nothing save the bicarbonate solution, or water, for the first twenty-four to seventy-two hours. Later we have given some form of cereal gruel and then diluted protein milk. The sugar has been kept low for some days and carbohydrate given mainly in the form of cereals.

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[17] For several months we have used the colorimetric apparatus devised by Marriott (Jour. Am. Med. Assn., 1916, **66**, 1594) which greatly simplifies the determination of carbon dioxid in alveolar air. A comparison with other methods has shown that the results are sufficiently accurate for all clinical purposes.

[18] This series of cases is still incomplete and will be the subject of a further report.

Owing to the frequent presence of sugar in the urine and a normal or increased blood sugar in these cases, we deem this procedure advisable.

SUMMARY

Infants suffering from severe diarrhea with toxic symptoms often show the following signs of acidosis: 1, decrease of the carbon dioxid of the blood and alveolar air; 2, decreased carbon dioxid combining power of the blood plasma; 3, high ammonia coefficient in the urine; 4, increased tolerance to sodium bicarbonate; 5 improvement of the symptoms after administration of sodium bicarbonate.

These signs are evident in some cases of diarrhea before the typical symptoms of intoxication have developed, and serve as a warning and therapeutic indication.

If an infant suffering from severe diarrhea has hyperpnea, the diagnosis of acidosis is almost certain. If hyperpnea is not observed the diagnosis of acidosis must rest on laboratory evidence.

Thorough and carefully controlled treatment by sodium bicarbonate usually causes disappearance of the acidosis, but despite this, the infants frequently die from a severe form of malnutrition.

We desire to thank Dr. L. E. La Fétra for the use of the material from his wards at Bellevue Hospital, and Drs. R. G. Freeman, C. G. Kerley and C. F. Collins for the cases from the Nursery and Child's Hospital. The determinations of the carbon dioxid combining power of blood plasma were made in the laboratory of Dr. A. O. Gettler at Bellevue Hospital, to whom we are indebted for this privilege and for much assistance.

FAMILIAL ICTERUS OF NEW-BORN INFANTS

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Pfannenstiel[1] gave the first detailed description of familial icterus of new-born children. He described two fatal cases and collected the scattered reports in the literature. The cause of familial icterus of new-born children is unknown. The disease has nothing in common with Buhl's or Winckel's disease. There is no evidence to prove that familial icterus is due to septic processes. It is not present at birth, but appears during the first days of life. In none of the cases is there a history of birth injury, nor does it seem to be due to toxemia of pregnancy. Most of these children are strong, robust and mature at birth. One might say that the children are in a sense physically defective and very soon become incapacitated to carry on extra-uterine existence. It is possible that the liver failed in the performance of its extra-uterine function.

The disease may occur in successive pregnancies. Occasionally normal children are born, and later children die a few days after birth as the result of a grave and progressive icterus. As a rule, there is no hereditary influence, nothing of a similar nature is discovered in the family of the father or mother. The disease begins usually on the first or second day of life and rapidly increases in severity. Pfannenstiel briefly described the symptoms by referring to the presence of catarrhal conditions of the mucous membrane, sometimes with bloody discharge, though true melena does not occur. The stools are catarrhal in character and are frequent; the urine contains bile pigment; the patient may show meningeal irritation, with characteristic crying and whining. At the onset there may be hyperemia of the skin. If the disease continues, hemorrhages from the various mucous surfaces and into the skin, as well as from the umbilicus, occur; death follows soon from collapse. Atonic convulsions, particularly of the upper extremities, as well as opisthotonos, are frequently observed. Pfannenstiel called attention to the fact that the disease bears no relation to syphilis, and in one case in which a necropsy was made and the liver and the spleen were examined histologically, no evidence of syphilis was discovered, and no spirochetes were found.

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* Read before the Twenty-Eighth Annual Meeting of the American Pediatric Society, held at Washington, D. C., May 8-10, 1916.

[1] Pfannenstiel, J.: Ueber den habituelle Ikterus gravis der Neugeborenen, München. med. Wchnschr., 1908, **55**, 2169, 2233.

Knopfelmacher,[2] who reviews the literature in a critical way, is inclined to think that after all some septic process might be invoked to explain this group of cases. For example, in one of Pfannenstiel's reported cases pericarditis, hemorrhages into the serous cavities and swelling of the kidneys led him to think that possibly an infection had taken place. He even thinks that the habitual occurrence of the disease in the same family is not sufficient argument against the consideration of sepsis. He considers that a chronic infection of the vaginal portion of the birth canal of the mother may serve as the origin of infection in the successive cases.

I should be inclined to believe from my own observation that the septic nature of this disease has not been proved.

The familial form of the disease is not a frequent one if we may judge from the reports of clinicians. Thus, H. Rehn[3] of Frankfort, in connection with a clinical report on one case, remarks that it is rare, and he states that in his fifty years' practice he had not met any similar cases until this one.

The disease under consideration, that is, familial icterus of the new-born, has nothing in common with chronic family jaundice, which is characterized by the fact that it may be present at birth, and it may persist throughout life, or that it may first occur during adolescence. In chronic jaundice the patient experiences but little inconvenience and may attain an advanced age. The enlargement of the spleen in chronic jaundice is a constant feature. Familial icterus of the new-born must also be differentiated from congenital obliteration of the bile duct. This obliterating disease is characterized by intense obstructive jaundice.

Isolated cases of habitual familial jaundice are described in the literature. McGibbon[4] records a family of six children, the oldest of whom was normal, the other five having jaundice. The fourth child was prematurely born; the other four children died of severe icterus between the third and seventh day of life.

Cornelius May[5] described a family in which the father and mother were perfectly normal, with no infections and no syphilis. The first child, born at full term and apparently normal, developed icterus in twelve hours and died on the third day. The second child, fairly well developed, born one year later, apparently normal, became icteric in six hours and died in two days. The third child, born three years later, apparently normal, developed intense icterus in twenty-four hours. The mother began to secrete breast milk on the third day, though the baby seemed too weak to nurse. The neck became rigid, the child cried and whined, convulsions occurred, and with increasing coma death followed on the twelfth day after birth. The necropsy showed no tissue changes or bacteriologic findings. The fourth child, born after three years, gives a very similar history. It developed icterus on the second day. The child was given breast milk, but gradually lost in weight, became comatose and died on the sixth day.

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[2] Knopfelmacher: Der habituelle Icterus neonatorum gravis, Ergebn. d. inn. Med. u. Kinderh., 1910, **5,** 205.

[3] Rehn, H.: Zur Kasuistik des habituellen familiären Ikterus der Neugeborenen, Jahrb. f. Kinderh., 1912, **75,** 358.

[4] McGibbon, John: Fatal Cases of Jaundice in the New-Born Child, with Notes of a Case in Successive Pregnancies, Edinburgh Obst. Soc., 1912-1913, **38,** 285.

[5] May: Beitrag zur Kenntnis des Ikterus Neonatorum gravis, Arch. f. Kinderh., 1911, **56,** 313.

Postmortem examinations have shown a peculiar icteric discoloration of the larger nuclei in the basilar portion of the brain and also a yellowish discoloration of the nuclei in the medulla. This has been described as nuclear icterus. In some instances the cells in the anterior gray portion of the spinal cord are stained yellow. Orth observed the same condition in the brain cells of children who suffered from the milder form of icterus neonatorum.

Pfannenstiel considers that the most important anatomic changes which exist in the so-called nuclear icterus (Kern icterus) are swelling of the spleen, hypertrophy of the liver without microscopic alterations in the structure of the organ, and a tendency to transudations into the serous cavities and into the ventricles of the brain. Catarrhal conditions of the mucous membranes in the digestive tract and minute hemorrhages on the serous and mucous surfaces are recorded, though fatty and other degenerative processes of glands and organs are absent.

I have encountered examples of familial icterus of the new-born in two families. The first case occurred in an Italian family. The baby in question was referred to me through the kindness of Dr. DeLee of the Chicago Lying-In Hospital and Dispensary. The history is as follows:

The mother and the father were 28 years of age. They were both born near Naples, the mother having lived in this country ten years and the father fifteen years, and they had been married nine years. The mother had pneumonia five years before and was very ill at that time. She had never had any surgical operation, and with the exception of the illness mentioned above, she had always been well. She had four brothers and one sister living and well and in none of their families had a similar diseased condition occurred. The mother's mother died the year before of pneumonia. The mother herself had been well during all of the previous pregnancies. The father's mother was living and well; his father died in Italy from some unknown cause. The father, a barber by occupation, said he had never been sick. The mother had borne five children, of whom two were living and three dead. In addition to this there had been two miscarriages, each occurring at three months. These constituted the second and fourth pregnancies. The first and the second babies were born well and remained so up to that time. The third baby seemed strong and robust at birth, but developed jaundice on the second day and on the third day the jaundice had deepened greatly, the baby being more or less comatose, having frequent convulsive attacks and dying on the third day. The fourth baby sickened on the second day, jaundice becoming intense, convulsions ensuing and death occurring on the third day, as in the previous case.

The family came under my observation with the birth of the fifth child. The history of the last baby does not differ materially from those already described. The child sickened on the first day, icterus became very marked, the child vomited occasionally, bowel movements became somewhat frequent, there was no elevation of temperature, convulsions occurred on the second day, and the child became comatose and died on the fourth day.

The second case occurred in a Russian Jewish family. The father had always been well and denied venereal infection. The mother had had the usual diseases of childhood. Six years before, on account of abdominal pain and symptoms referable to the gallbladder, an operation was performed and the gallbladder was removed. Two or three months after this operation her tonsils were removed. The mother was about 32 years of age and the father was three years her senior. She had borne six children. When her first baby was born the mother was about 21 years of age. This child, a boy, is living and is 11 years old. He had scarlet fever when 6 years of age. His urinary examination shows albumin and casts, and he has a chronic nephritis. The second child is living and well. The third pregnancy resulted in a miscarriage. The fourth child was born robust, but became jaundiced on the second day, was seized with convulsions, had frequent stools, the jaundice became more and more intense, and he died on the third day. I was enabled to examine the fifth child. The mother was delivered at Michael Reese Hospital in May, 1914, in the service of Dr. Lester E. Frankenthal. The child was born apparently well and strong. On the first day he developed jaundice, which rapidly became intense; hemorrhages occurred from the nose and throat and under the skin, and convulsions took place at intervals; vomiting and diarrheal stools were observed, and the baby died on the third day. A necropsy was performed, which showed some enlargement of the liver and spleen, though no other pathologic changes of any moment could be noted and bacteriologic examinations showed the tissues to be sterile. The bile passages were of normal size and showed no obstruction.

The sixth baby was born April 22, 1915, in the service of the Chicago Lying-In Hospital and Dispensary. Delivery was rapid and easy, and there was no asphyxia at birth, the child crying vigorously. The baby became icteric on the second day. The umbilical wound was normal. The child voided bile-stained urine, but had the normal number of stools. The temperature was about 99. The child resented palpation of the abdomen, and it was thought that there was some tenderness over the liver. The baby cried much and the jaundice deepened materially. The child slept most of the time, nursed very poorly, did not take water, and whined weakly. The conjunctivae became icteric and the yellowness of the skin increased markedly. The urine decreased in quantity, the temperature remained at 99, and the baby seemed very somnolent and toxic. There were no petechial spots and no hemorrhages. On the fourth day the temperature was still 99 and the icterus was more marked. The baby refused food, except as it was forced. The liver was enlarged, but the spleen was not palpable. The somnolence increased and the condition seemed grave. On the fifth day the baby had improved slightly, but icterus was still marked. The child took food more readily, and the urine was voided more frequently and in larger quantities. The baby seemed better, and from this time on the jaundice disappeared gradually. The baby nursed more normally and continued to improve. The child is now over a year old and seems unusually bright and happy, having had no illness of any consequence since then.

CONCLUSION

These reports relate the occurrence of a rare disease in new-born children, characterized by progressive icterus occurring in successive pregnancies and of unknown origin. The disease nearly always terminates fatally, though one of my patients recovered after a most serious attack and with the most alarming symptoms.[6]

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[6] In addition to the references already given, the following will be found of interest:

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THE CALCIUM METABOLISM IN A CASE OF HEMOPHILIA *

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C. E., 9 years old, entered the hospital because of sudden enlargement of the right knee. He gave a history of repeated attacks of purpura, at times associated with vomiting and fever. The coagulation time of the blood was found to be two and one-half hours. Shortly after entrance he had a marked attack of purpura, with vomiting and fever; and during his stay in the hospital he had many spontaneous and subcutaneous hemorrhages. His brother, aged 19, was also under observation during part of this time for spontaneous hemorrhage into one knee.

A history of bleeding was obtained as follows: Of this family of twelve children, six girls and six boys, three of the boys were bleeders, one dying in infancy from hemorrhage. The maternal grandmother was a bleeder, and was one of ten children, four girls and six boys, three of whom were bleeders, herself and two brothers. The maternal great grandmother and her brother were the only bleeders in a family of seven children, five girls and two boys; her father (patient's great great grandfather) was a bleeder. Of the patient's family, in the order of birth, the third, fourth and eleventh male children were bleeders, the patient being the eleventh.

These data establish the case from the clinical side as one of hemophilia, with the characteristic transmission coming from the female side through two generations.

The coagulation time was determined by taking 3 c.c. of blood directly from a vein into a 10 c.c. test tube. It was placed in the incubator at 37 C. and carefully examined from time to time until the first definite appearance of clotting was observed (see table). During the control period the average coagulation time was two and one-half hours; during the third and fourth day of the calcium feeding period the coagulation time was lengthened two hours. The calcium content of the blood was increased over the control period at this time, as will be seen from the table. During the second control period, that is, after discontinuing the calcium, the coagulation time again returned to two and one-half hours.

The calcium determinations in the blood, urine, feces and food extended over a period of fourteen days. The patient was given a cathartic and put on a milk diet, 7 ounces (210 c.c.) accurately measured every two hours for eight feeds, or 56 ounces (1,680 c.c.) daily. The child was kept on this diet for two days before the determinations began.

H. Lyman's[1] turbidity method was employed for the calcium determinations. In the case of the feces, blood, and milk we substituted and adapted to our use an oxidation method in place of the incineration method usually used. This method was originated by Professor Willard of the department of chem-

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* From the Department of Pediatrics, University of Michigan Medical School.

[1] Lyman, H.: Jour. Biol. Chem., 1915, **21,** 551.

istry for the estimation of the mineral content of coal and other organic material, the details of which are not yet published.

The first five days' determinations constitute the first control period, the following days the calcium feeding period, during which the patient received calcium lactate, as indicated in the table. Thirteen per cent. of calcium lactate is calcium. Twenty-six gm. of calcium lactate was to have been given dissolved in distilled water. This was equivalent to 3 gm. of calcium. After the first dose of 7 gm. of calcium lactate the patient complained of considerable epigastric pain, and vomited a small amount. The calcium had to be discontinued. On the seventh day 12 gm. of calcium lactate was to have been given in divided doses of 4 gm. each, but after the first dose the same symptoms recurred. The patient was then given a one-day period of rest from the lactate, during which the milk diet was continued. No determinations were made on this day.

Calcium Determinations in the Food, Urine, Feces and Blood

Day	Period	Food (Milk)		Urine			Feces		Calcium in 1,000 C.c. Blood, Gm.	Coagulation Time, H. M.
		Per Cent. Calcium	Total Calcium, Gm.	C.c.	Per Cent. Calcium	Total Calcium, Gm.	Weight, Gm.	Total Calcium, Gm.		
1	Control	0.343	5.0421	297	...	0.10048	32.01	0.5479	....	....
2	....	0.322	5.2245	1,030	...	0.482	....	....	0.6482	2:35
3	....	0.344	5.3804	320	...	0.2322	....	....	0.6828	2:32
4	....	0.329	5.3742	1,044	...	0.7471	128.6972	3.4045	0.66	2:48
5	....	0.345	5.3944	832	8†	0.5578	....	....	0.6866	2:35
6	Calcium *	0.349	5.5522	545	...	0.3777	63.334	1.85644	0.6274	1:50
7	*	0.347	5.4256	545	...	0.3277	110.9778	2.4282	0.658	3:30
8	....	......	....	......	...	....	....	....	....	....
9	0.65 gm.	0.351	5.9085	744	...	0.5016	277.02	6.7102	0.665	3:00
10	0.91 gm.	0.343	5.4537	855	...	0.5921	....	....	0.6844	2:38
11	1.17 gm.	0.345	5.8111	635	...	0.4519	37.338	0.6372	0.7192	4:55
12	1.56 gm.	0.344	5.7926	942	1.5	0.6337	92.141	2.3703	0.7545	4:35
13	Control	0.344	5.7879	772	...	0.5241	260.1684	2.7117	0.6918	2:45
14	....	0.345	5.8044	797	8	0.5102	99.875	1.814	0.6612	2:15

* The patient vomited the calcium lactate. The calcium was calculated as 13 per cent of the lactate.
† Percentage of total periods.

On the ninth day the patient was given 1 gm. of calcium lactate every two hours for five doses, which is equivalent to 0.65 gm. of calcium. On the tenth day 7 gm. of calcium lactate were given, 0.91 gm. of calcium. On the eleventh day 9 gm. of calcium lactate were given, 1.17 gm. of calcium; and on the twelfth day were given 12 gm. of calcium lactate, 1.56 gm. of calcium. This was followed by a control period of two days.

The accompanying table records the determinations made. The calcium content of the food (milk) was quite constant, as will be seen from the percentage of calcium in milk given in the table. It should be stated that these estimations make the calcium content of milk slightly higher than the figures usually given, which are from 0.149 to 0.198 per cent. The calcium content of the urine was apparently unchanged by the administration of calcium by the mouth. The blood calcium increased perceptibly but slightly during the calcium feeding period. The data obtained from the feces are of doubtful value, not because of the method of analysis, but because of our inability to obtain daily stools on account of constipation, and because we erred in that we did not mark the stools. We hoped that the preliminary period of milk feeding before the estimations were begun and the long periods of control and of calcium feeding would enable us to obtain averages which would be of more value than one or two day observations. We were particularly interested in the blood calcium and these data, like those of the milk and urine, we believe are trustworthy and of value.

The following conclusions seem to be justified:

1. The calcium content of the blood in this case of hemophilia is the same as that obtained under normal conditions.

2. The calcium content of the blood increased perceptibly during the calcium feeding period.

3. The coagulation time of the blood was lengthened during the calcium feeding period.

4. The calcium content of the food (milk) was slightly greater in our series than in the usually reported analyses.

THE CEREBROSPINAL FLUID IN POLIOMYELITIS

WITH ESPECIAL REFERENCE TO THE LANGE REACTION *

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ST. LOUIS

Early in poliomyelitis, before the onset of paralysis, or in those abortive cases which do not develop paralysis, there is found no pathognomonic diagnostic feature either at the bedside or in the laboratory. The clinical picture and history are usually fairly uniform and striking, but these same symptoms and signs are of such frequency in other infections that a reliable diagnosis cannot be made from them alone. The nearest evidence of a positive nature as to the presence of this infection in a preparalytic or abortive case is secured by the correlation of the clinical data with the results of examination of the cerebrospinal fluid.

The characteristics of cerebrospinal fluid in the early stages of poliomyelitis will be briefly summarized. It is clear and increased in amount. From 15 to 60 c.c. or more may be readily withdrawn. It frequently shows a marked web formation. The reduction of Fehling's solution is prompt, as in a normal fluid. There is a slight to moderate increase in the albumin, globulin and cellular elements. The cell counts vary from practically normal in a few cases to 500 or more per cubic millimeter, the majority having less than 200 cells per cubic millimeter. Eighty per cent. or more of these cells are mononuclears.

There are three rare types of cerebrospinal fluid found. One of these is a slightly cloudy fluid which shows a polymorphonucleosis, usually about 60 per cent., but which may be as high as 90 per cent. The other two types occur when the hemorrhagic process has been more than usually extensive. One of these has blood evenly diffused throughout the fluid, and the other, though having no blood cells, has a yellow color and coagulates spontaneously. The latter type has recently been present in our St. Louis material.

Conditions which may be confused with preparalytic or abortive poliomyelitis are *meningism, syphilis* and meningitis, either *tuberculous* or *purulent*.

In meningism is found a fluid increased in amount but normal in character, and the underlying infection is usually manifest after a short interval, if not at the first examination.

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In syphilis of the central nervous system there is usually found a fluid identical with that of poliomyelitis. However, in syphilis the fluid gives a positive Wassermann reaction and there is rarely if ever an acute onset with fever in children.

In purulent meningitis, even in the early stages, there is usually some degree of cloudiness from cellular increase and the cells are 90 per cent. or more polymorphonuclears. In certain mild cases of the epidemic variety the organism may never appear, but in the other varieties it will practically always appear, if not present at the first examination, as further punctures are made.

The differential diagnosis of poliomyelitis from tuberculous meningitis will often present difficulties. In both conditions the fluid is usually clear. The increase in the albumin, globulin and the cellular elements is usually greater in tuberculous meningitis than in poliomyelitis. The reduction of Fehling's solution is usually better in poliomyelitis, though many fluids from tuberculous meningitis reduce Fehling's solution readily, especially if obtained early in the disease. In both conditions there is usually mononucleosis, although in some cases of tuberculous meningitis there is a polymorphonucleosis. By careful search, tubercle bacilli may be found in 90 per cent. or more of fluids from tuberculous meningitis. In the remaining cases, animal inoculation and the clinical course of the disease must be depended on. Tuberculous meningitis seldom has the acute onset and high fever that accompany poliomyelitis. By correlating the laboratory findings with the clinical picture the differential diagnosis is usually not difficult, though several cases are recalled in which the diagnosis was later proved to be in error.

Since there is no one laboratory measure that is pathognomonic of this disease, it seems advisable to extend the laboratory examination as much as would prove helpful in arriving at a definite diagnosis. The Lange colloidal gold reaction has been observed by one of us on a small number of fluids from patients in cases of poliomyelitis occurring sporadically in St. Louis.[1] In these cases the occurrence of an early transitory reaction in the "syphilitic zone" in the acute stage suggested an important aid in the diagnosis. In order to study the reaction in a larger number of cases, Lange colloidal gold tests were made with fluids from patients in 100 cases occurring in the 1916 New York epidemic (Table 1).

Fifty-five of these patients had symptoms, including paralysis, which were sufficient evidence that they had poliomyelitis. In the fluids from the entire fifty-five there was definite reduction of the colloidal gold solution with the lower dilutions of spinal fluid. This reaction occurred in a fairly uniform and regular manner, just as had happened previously in a smaller number of sporadic cases in St. Louis. In seven of these cases the Noguchi test gave a doubtful result (±) for globulin. In five of the seven there was no increase, or only very slight increase, in the cells. So that even in those cases of undoubted poliomyelitis in which there was apparently no change in the spinal fluid as far as the usual methods of examination show, the Lange test showed definite changes and was the only good evidence, aside from paralysis, that the cases were poliomyelitis.

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[1] Johnston, M. R.: A Study of Normal and Pathologic Cerebrospinal Fluids in Children, Am. Jour. Dis. Child., 1916, **12**, 112.

The number of cases seen without paralysis, but which later developed paralysis, is not definitely known, but several are known to have progressed in this manner following the first lumbar puncture at which the material for this study was obtained, and in these cases the colloidal gold reaction was essentially no different in the preparalytic stage from that obtained after paralysis had developed.

Abortive cases which never become paralyzed are known to occur with considerable frequency. With the usual symptoms of onset and a cerebrospinal fluid that presents increased globulin and cells, a diagnosis of poliomyelitis is justified even in the absence of paralysis. In all such cases in this study the colloidal gold reaction was similar to that of the paralytic cases.

In cases presenting the usual symptoms of onset, not developing paralysis, and in which the cerebrospinal fluid showed no increase in the globulin, and slight or no increase in cells, but causing the usual colloidal gold reaction, it is to be concluded that these were cases of abortive poliomyelitis. It is in such cases that the Lange reaction shows its greatest usefulness. In this small series there were four such cases and two others having an increase in cells, but a doubtful globulin test. A Lange reaction is good evidence that a spinal fluid is pathologic and is sufficient to differentiate between poliomyelitis and meningismus or any other condition giving a normal cerebrospinal fluid.

The occasional difficulty of differentiating between a fluid from poliomyelitis and one from tuberculous meningitis is not made absolutely conclusive by the colloidal gold reaction. As is seen in the accompanying table (Table 2), fluids from cases of tuberculous meningitis cause the greatest changes in the middle dilutions, while the greatest changes caused by a fluid from poliomyelitis are in the lower dilutions. A distinct limitation of the maximum intensity to these zones is not constant in either condition. However, fluids from cases of poliomyelitis which cause a maximum change in the "Middle zone" at the same time produce changes in the lower dilutions — which is not the case with fluids from tuberculous meningitis. The variations in these reactions are so rare that we believe the colloidal gold reaction is

TABLE 1.—RESULTS OF EXAMINATION OF CEREBROSPINAL FLUID IN 100 CASES OF POLIOMYELITIS *

No.	Lange Reaction	Albumin	Globulin (Noguchi)	Sugar (Fehling)	Cellular Increase†	Mononuclear, %	Amt., C.c.	Age, Years	Day of Disease	Remarks
2570	1112331000	++	+ 1	+++	Gt.	98	20	25	4	Paralysis of both lower extremities
2571	1123310000	++	++	+++	Mod.	70	10	32	4	Paralysis of left quadriceps and right leg
2573 2791	1112200000 1122210000	++ +	++ + 1	+++ +++	No Sl.	.. 100	35 ..	5 5	19 30	Temperature 101 on day of admission, 14 days after onset; no paralysis
2574	1124300000	++	+ 1	+++	No	98	40	4	9	No paralysis; tenderness over spine; rigidity of back; temperature normal
2575	1122110000	+	±	+++	Sl.	98	30	4	13	No paralysis; temperature normal
2600 2760	1221000000 1232120000	+ 1 + 1	+ 1 ++ 1	+++ +++	Sl. Sl.	95 100	25 15	Infant ..	8 17	Weakness of muscles of shoulder, neck and back on right side
2601	1122110000	+ 1	++	+++	Sl.	95	25	3	8	Paralysis of right upper and both lower extremities; temperature normal
2602	1122200000	++	+ 1	+++	Mod.	98	25	..	13	Paralysis left deltoid; rigidity of neck
2610 2762	1112100012 1233110000	++ +	++ +	+++ +++	Mod. Sl.	.. 100	25 10	3 ..	12 21	Temperature normal at time of puncture; no paralysis; had a general tremor
2611 2765	1221100000 1112220000	++ 1 + 1	++ 1 ++	+++ +++	Mod. Sl.	90 ..	30 15	2½ ..	13 22	Temperature slightly elevated; Kernig and Macewen signs elicited; paralysis of left leg
2612 2764	1122110000 1123331000	++ 1 + 1	++ 1 ++	+++ +++	Sl. Mod.	.. 100	10 12	2 ..	12 21	Temperature normal; weakness of left quadriceps extensor
2614 ‡	1122100000	++	+	+	Mod.	90	..	1½	7	Child had never walked; had general weakness of long standing; hyperesthesia and general irritability at onset; high temperature on third and fourth days; no rigidity; Macewen sign doubtful; no paralysis
2615	1122210000	+	+	+++	Gt.	98	30	3	4	No paralysis; delirious; Macewen sign; tenderness along spine
2617 2780	1112100000 1123210000	++ ++	++ ++	+++ +++	Gt. Mod.	98 100	12 20	6 ..	6 15	No paralysis; temperature normal; clinically diagnosed "no case"
2618	1123210000	++	+ 1	+++	Mod.	98	35	4	6	No paralysis; slight fever; weakness right leg 4 days later
2619	1123310000	+ 1	+ 1	+++	Gt.	99	15	3	9	Clinically diagnosed tuberculous meningitis; later appeared weakness of right shoulder; recovered
2623	1111000000	+	+	+++	Mod.	95	25	6½	4	Double ptosis; eye movements not coordinate; unable to swallow; weakness left deltoid, neck and back; diaphragmatic respiration. Died on fourth day
2625	1123210000	+ 1	+ 1	+++	Gt.	90	25	2⅓	3	Temperature 102; paralysis of both upper and lower extremities
2626	1123321000	+ 1	+ 1	++	Gt.	95	25	2	3	Paralysis of back, both deltoids and both lower extremities
2628	1122210000	+ 1	+ 1	++	Mod.	90	12	3	4	Died same day; diaphragmatic paralysis
2630	1123321000	+ 1	+	+	Mod.	95	12	6	7	Temperature normal; weak right arm and weak neck
2631	1121000000	+	±	+++	Sl.	90	25	1	3	Temperature 101; weak neck, back and deltoids; paralysis of quadriceps

2632	1123300000	+ 1	+ 1	+++	Mod.	90	18	1½	1	Temperature 103; developed paralysis of both legs
2633	0111100000	++	++	+++	Gt.	90	15	1½§	..	Paralysis both arms and legs, neck, back and right facial. Died third day
2634	1121000000	+	+	+	Gt.	90	12	4	3	Temperature 101; paralysis of left deltoid
2636	1122210000	++	+++	+++	Sl.	90	15	¾	2	Weak neck and back; paralysis of both legs
2639	0112210000	++	+ 1	+++	No	..	30	28	6	Temperature 100; previously higher; drowsiness; general weakness, especially of back; Wassermann reaction negative; clinical diagnosis, hysteria; five days later had Rombergism and weakness of right facial
2640	1122100000	+	+	+++	Sl.	90	15	..	..	Died; no paralysis; question of tuberculous meningitis
2641	1111000000	+	±	+++	Sl.	..	25	1½	4	No paralysis; onset with headache, vomiting, temperature 103; at time of puncture temperature 100, hyperesthesia, rigidity of neck; Macewen sign; tenderness over spine
2644	1121000000	+++	+++	+++	Mod.	95	12	3	4	No paralysis; onset sudden with temperature 103, headache and apathy; at time of puncture temperature 98.2; hyperesthesia; irritable; rigidity of neck; Macewen and Kernig signs elicited
2645	1122100000	+ 1	+ 1	+++	Gt.	90	35	2	2	No paralysis; onset with temperature 105; vomited once; at time of puncture slight rigidity of neck; hyperesthesia, tenderness over spine; Macewen
2646	1111000000	+	+	+++	Gt.	40	20	9	2	No paralysis; onset with temperature 103; vomiting and apathy; at time of puncture temperature 102; hyperesthesia; rigidity of neck; Macewen and Kernig signs positive
2647	1122100000	+	+	++	Mod.	95	20	3	6	Temperature 102.4; rigidity of neck and back; weak quadriceps; later thoracic paralysis
2648	1111000000	+	+	++ 1	Sl.	90	13	2	5	Paralysis left deltoid and both legs; later died of respiratory paralysis
2649	1122100000	+ 1	+ 1	++	Mod.	90	20	..	3	Paralysis both deltoids and quadriceps; temperature 101 to 104; later intercostal paralysis
2652	1121000000	+	+	++	Gt.	98	30	7	..	Probably poliomyelitis; no paralysis
2653	1111000000	+	±	+++	Mod.	90	30	2	..	Probably poliomyelitis; no paralysis
2654	2231000000	±	±	++	Sl.	95	10	2	5	Probably poliomyelitis; no paralysis; temperature normal
2655	1111100000	+	+	++	Mod.	98	..	6	3	Paralysis without previous illness
2661	1123110000	+	+	+++	Gt.	98	50	8½	5	Paralysis flexors left arm; rigidity neck and back; pain back and legs
2662	1121000000	+	+	+++	Gt.	95	..	7	1	No paralysis; fever, headache, vomiting; rigidity of neck
2664	1122110000	++	++	+++	Mod.	98	15	1½	7	Paralysis of right leg; temperature normal
2667	1111000000	+	+	+++	Sl.	95	25	2	16	Left facial paralysis; temperature normal; later right deltoid paralysis
2668	0125533510	++	++	+++	Gt.	99	20	2	2	Fever, stupor, tenderness over spine; later paralysis right leg and both arms
2669 }	1123332000	++	++ 1	+++	Gt.	98	..	5	3	} Onset with temperature 103; vomiting and headache; rigidity of neck; temperature 101.2; partial paralysis both legs; irritable
2724 }	0123210000	+++	+++	++	No	..	..	..	6	
2677	2233310000	+++	++ 1	+++	Mod.	99	18	5	5	Temperature slightly elevated; paralysis of left leg

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* For the nonparalytic cases in which information was obtainable there is appended a brief of the clinical data.

† The abbreviations denoting cellular increase indicate as follows: Sl. = slight increase, i. e., from 10 to 50 per c.mm.; Mod = moderate increase, i. e., from 50 to 150 per c.mm.; Gt. = great increase, i. e., above 150 per c.mm.

‡ 2614. Fluid from previous puncture bloody. This specimen shows a few red blood cells.

§ 2633. Age 1½ months.

TABLE 1.—RESULTS OF EXAMINATION OF CEREBROSPINAL FLUID IN 100 CASES OF POLIOMYELITIS *—(*Continued*)

No.	Lange Reaction	Albumin	Globulin (Noguchi)	Sugar (Fehling)	Cellular Increase†	Mononuclear, %	Amt., C.c.	Age, Years	Day of Disease	Remarks
2678	1122100000	+	±	++	Sl.	100	7	2	2	Temperature 102; rigidity of neck and back; right facial paralysis
2679	2333233100	++ 1	++	+++	No	..	18	⅚	3	Temperature 101; paralysis both legs and left arm; died fifth day of respiratory paralysis
2680	1234310000	++	++	+++	Sl.	100	30	4½	2	Temperature normal; no paralysis; rigidity of neck and back; opisthotonus
2681	0112333111	+++	+++	+++	No	..	35	2	..	Rigidity neck and back; paralysis quadriceps and intercostals; died ninth day
2682	2333311000	+	+	+++	Mod.	100	35	3½	3	Onset with vomiting and temperature 102; left facial paralysis; Kernig; rigid neck
2683	1111100000	+ 1	+ 1	+++	Sl.	..	..	12	..	Clinical diagnosis, meningeal irritation due to injury; observed and punctured 8/16/16; had a fall 7/4/16; improved to two weeks ago when he began to feel bad again; much worse past few days; stuporous; Macewen and Kernig; clonus right ankle; on 10/14/16 report of complete recovery
2685	1112321000	++ 1	++ 1	+++	Mod.	95	35	1	7	Onset with gastro-enteritis; fever and prostration since; comatose; died seventh day of "respiratory paralysis"
2689	1122100000	+	+	++	Gt.	99	25	3¾	..	Paralysis both arms, legs, neck, voice and respiration; died sixth day
2695	1121100000	+	±	+++	Sl.	90	..	2⅔	3	Irritable; hyperesthesia; Macewen; questionable weakness right leg; (onset with temp. 103; headache, vomiting and apathy)
2696	1122200000	+	+	++	Mod.	98	..	2½	6	Temp. 102; hyperesthesia; increased reflexes; rigidity of neck; Kernig and Macewen positive; no paralysis; sudden onset with fever
2697	1112110000	+ 1	+ 1	++	Gt.	95	25	..	..	Clonic convulsions; probably poliomyelitis
2698	1222200000	++	+ 1	+++	Gt.	98	30	1½	7	No paralysis; temperature normal; neck rigid; Macewen positive; tenderness over spine; (sudden onset with temp. 103.5)
2703	1122110000	+	+	+++	Mod.	50	25	..	5	Paralysis; Macewen positive; died day of puncture
2704	1123220000	+	+	+++	Mod.	99	20	..	4	Moribund at time of puncture; died of respiratory paralysis
2705	1122210000	+	+ 1	+++	Sl.	98	15	..	4	Paralysis; died
2706	1122100000	+	+	+++	Gt.	100	20	..	8	Moribund; paralysis; died
2708	1122220000	+	+	+++	Mod.	100	15	..	3	Moribund at time of puncture; Macewen positive; reflexes absent; died
2715	±112330000	++	+++	+++	Mod.	100	..	..	2	Continued high fever; no paralysis; comatose; neck rigid; Kernig and Macewen positive; history of pertussis for two weeks; clinical diagnosis of tuberculous meningitis had been made; no tubercle bacilli found in fluid; died few hours after puncture
2717	1122100000	+	+	+++	Sl.	98	25	⅔	4	Temperature 101; paralysis of both legs
2718	1112331000	+	+	+++	Gt.	99	20	⅙	3	Temperature 100; rigidity of neck and back; question of anterior tibial paralysis
2720	1112331000	+++	++	+++	Sl.	100	12	¼	3	Died; paralysis respiratory muscles and of both arms and legs
2723	1233200000	+	+	+++	Mod.	99	30	3½	4	Fever; no paralysis; tremors and slight spasticity left leg
2725	1123331000	++	++	+++	Mod.	100	12	Adult	7	Paralysis of both legs
2729	1232200000	+	+	+++	Sl.	100	30	5	7	Temperature 99; left facial paralysis

2730	1133310000	+ 1	+ 1	+++	No	..	25	1¼	9	Paralysis left deltoid; (sediment shows slight blood)
2733	1123210000	++ 1	++ 1	+++	Gt.	98	40	13	5	Temperature 101; no paralysis; improving
2734	1122210000	+++	+++	+++	Sl.	100	40	3	21	Temperature 102 on third day; now stuporous; weakness right leg and right side of face
2738	1110000000	+	+	+++	No	100	30	..	..	No paralysis; question of poliomyelitis; had malaria
2740	0132200000	++	++	++	Gt.	100	20	8½	5	Onset with vomiting, headache and fever; temperature now 102; hyperesthesia; difficulty in swallowing; Macewen and Kernig signs positive
2741	1112100000	+	+	+++	Mod.	98	20	..	4	No paralysis; temperature 98.2; apathy; Macewen; rigidity of neck; onset with vomiting, headache and temperature to 102
2755	1233210000	+ 1	+ 1	+++	Gt.	100	25	10	1	Temperature 105; bulbar paralysis; delirium
2769	1122100000	+	±	+++	Gt.	100	25	..	4	Illness followed fall from window to floor; fall at 6:30 p. m.; vomiting in the night; fever next morning, with rigidity of neck and positive Kernig; increased reflexes; no paralysis
2770	1112210000	+++	+++	+++	Sl.	100	25	..	24	Paralysis of left arm and both legs
2771	1112320000	++	+ 1	+++	Sl.	100	15	23	43	Had facial paralysis for one day
2772	1232210000	+	+	++	Mod.	98	30	2	47	Paralysis of both legs; practically well
2773	1123100000	+	±	+++	Mod.	..	40	4	42	Full recovery; had weakness right leg and rigidity of neck and back
2774	1232210000	+	+	+++	Sl.	100	40	5	..	Paralysis left thigh, weakness of right; slight left foot drop; (discharged well eighth week)
2775	1111100000	+	+	+++	Mod.	..	10	6	47	Paralysis, left facial; tremors left thigh and both hands; complete recovery
2776	1123310000	+	+	+++	Mod.	100	..	..	11	Questionable poliomyelitis clinically; had chorea
2777	1122110000	+	+	+++	Gt.	100	20	..	..	Early cases at Queensborough Hospital; paralytic
2778	1123310000	++ 1	++ 1	+++	Mod.	100	18	..	..	
2779	2223110000	+	+	+++	Mod.	95	20	..	..	
2787	1112200000	+ 1	+	+++	Mod.	98	15	1	6	Temperature 100.8; no paralysis; Macewen positive; onset with vomiting and temperature 102
2788	1111000000	+	+	+++	Mod.	100	25	2	2	Temperature 100.8; no paralysis; Macewen positive tender spine; temperature at onset 104
2792	1132210000	+	±	+++	No	..	50	..	12	Paralysis of left leg
2793	1111100000	+	+ 1	+++	Gt.	98	30	..	..	Doubtful diagnosis clinically; question of typhoid
2794	1122200000	++	+	+++	Gt.	100	20	7	3	No paralysis; rigid neck; onset with vomiting, headache and temperature 104
2795	1123210000	++	++	+++	Mod.	99	50	1	4	Rigidity of neck; strabismus; Macewen; onset with vomiting and fever
2796	1112221000	++	++	+++	Mod.	99	40	4	4	No paralysis; irritable; hyperesthesia; rigid neck; tender spine; Macewen and Kernig positive; onset with vomiting and fever
360	1122100000	±	±	+++	No	..	25	..	2	Paralysis present
386	1121100000	+	+	+++	Sl.	98	10	..	2	No paralysis; (later had weakness of legs)
391	1112100000	+	+	+++	Sl.	98	25	..	4	Paralysis of right arm and leg
396	1233100000	+	+	+++	Mod.	97	15	..	17	Left facial paralysis
401	±112100000	+	±	+++	Mod.	98	..	..	17	Paralysis present

a distinct aid in the differentiation of these two conditions, before the clinical picture is entirely clear.

Products in the cerebrospinal fluid of a purulent process in the brain or meninges cause colloidal gold changes in the higher dilutions, thus being quite different from the changes produced by a fluid from poliomyelitis. The other cerebrospinal fluid changes resulting from the various purulent infections, however, are usually such that a Lange test is quite unnecessary.

TABLE 2.—A Few Selected Tests in Tuberculous Meningitis and Poliomyelitis Showing the Usual Reactions and the Extreme Variations

Tuberculous meningitis	Poliomyelitis
±± 1 2 4 4 2± 0 0	1 1 2 3 3 2 1 0 0 0
±± 1 3 3 2± 0 0 0	1 1 2 3 3 3 1 0 0 0
±±± 2 5 5 5 1 0 0	1 1 1 2 3 2 0 0 0 0
± 1 2 4 4 4± 0 0 0	1 1 1 2 3 3 1 0 0 0
± 2 4 4 2 2± 0 0 0	1 1 2 2 1 0 0 0 0 0
0 0 0 2 3 3 2 0 0 0	1 1 2 3 2 1 0 0 0 0
0 0± 5 5 3± 0 0 0	1 2 2 1 0 0 0 0 0 0
0 0 0 3 4 4 4 0 0 0	1 1 2 1 0 0 0 0 0 0
1 1 1 4 4 4 4 1 0 0	

SUMMARY

The colloidal gold reaction with cerebrospinal fluid from patients with poliomyelitis has been recorded in isolated instances, and by one of us in a small number of sporadic cases occurring in St. Louis. The results in these few cases indicated that this reaction might be of service in the diagnosis of this disease. In order further to investigate this point, cerebrospinal fluids from patients in 100 cases occurring in the recent New York epidemic were examined, and it is the object of this paper to record the results.

From these results it is to be concluded that the colloidal gold reaction is of distinct service in the diagnosis of poliomyelitis. The greatest usefulness of the reaction is in showing to be pathologic a fluid which does not give other evidence of abnormality when examined as to its albumin, globulin and cellular content. This evidence of abnormality is most useful in those cases of poliomyelitis in which there are the usual symptoms of onset and in which paralysis has not developed. It is also our belief that the Lange reaction is of service in differentiating between poliomyelitis and tuberculous meningitis, between which diseases there not infrequently arises for a time a confusion as to diagnosis.

THE SCHICK TEST IN POLIOMYELITIS, SCARLET FEVER, MEASLES AND IN NORMAL CHILDREN

ITS BEARING ON THE QUESTION OF NATURAL IMMUNITY *

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The routine employment of the Schick test in children with poliomyelitis admitted to the Willard Parker Hospital during the recent epidemic established a most interesting and significant fact. This, in conjunction with some previously published observations on the Schick reaction in normal children and in children suffering from scarlet fever, and some more recent observations with the test in cases of measles, may throw some light on the still open question of natural immunity and suceptibility of individuals to infectious diseases.

From a previous communication on the Schick reaction[1] the accompanying tables (Tables 1 and 2) are taken.

TABLE 1.—Summary of Schick Tests in 2,700 Normal Children

Age, Years	Total	Negative Schick	Positive Schick	Per cent. Positive Schick
2 to 4	62	42	20	32.2
4 to 6	318	236	82	25.7
6 to 8	444	347	97	21.8
8 to 10	597	462	135	22.6
10 to 12	584	459	125	21.4
12 to 14	506	416	90	17.7
14 to 16	189	158	31	16.4
	2,700	2,120	580	21.4

The tables show the results obtained with the test on a large series of normal children and scarlet fever patients. It is interesting to note that normal children between the ages of 2 and 4 years show about 32 per cent. of positive reaction, as compared with scarlet fever patients, of whom about 65 per cent., or more than twice as many children, gave a positive reaction.

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* Submitted for publication Dec. 23, 1916.

* From the Department of Health, City of New York.

[1] Park, W. H., and Zingher, Abraham: Diphtheria Immunity. Its Determination by the Schick Test, Am. Jour. Pub. Health, 1916, **6**, 431.

TABLE 2.—Schick Reactions Among Scarlet Fever Patients

Age, Years	Total	Negative Schick	Positive Schick	Per cent. Positive Schick
½ to 1	10	5	5	50.0
1 to 2	68	22	46	67.6
2 to 4	223	93	180	65.9
4 to 6	249	116	133	53.4
6 to 8	196	123	73	37.2
8 to 15	237	171	66	27.8
Over 15	167	126	41	24.5
	1,200	656	544	45.3

TABLE 3.—The Schick Test in Measles Cases

Age, Years	Total	Negative Schick	Positive Schick	Per cent. Positive Schick
Up to 1	35	25	10	28.6
1 to 2	53	35	18	34.0
2 to 4	64	37	27	42.1
4 to 6	44	29	15	34.0
6 to 8	17	14	3	18.2
Total	213	140	73	34.2

Table 3 gives the results with the Schick test obtained in a series of 213 cases of measles. This table shows that between the ages of 1 and 4 years only about 10 per cent. more of the children gave a positive reaction than normal children of the same age group.

Table 4 shows the results with the Schick test in 1,350 poliomyelitis cases. Between 1 and 4 years of age there is an average of over 80 per cent. of positive reactions. This percentage is based on over 1,000 cases and can, therefore, be accepted as being fairly accurate. It was interesting and striking to see in the wards of the Willard Parker Hospital row after row of children who gave a positive Schick reaction. Indeed, at one time the number of positive tests in this age group reached between 90 and 95 per cent.

What are the significant facts to be found in the four tables? They give the results of tests in fairly large series of cases and are, therefore, probably correct. Such a preponderance of individuals susceptible to diphtheria among cases of poliomyelitis and scarlet fever suggests one of two possible causes:

TABLE 4.—The Schick Test in Poliomyelitis Cases

Age, Years	Total	Negative Schick	Positive Schick	Per cent. Positive Schick
Up to ¼	11	9	2	18.2
¼ to ½	30	20	10	33.3
½ to 1	150	32	118	78.7
1 to 2	529	92	437	82.6
2 to 4	425	88	337	79.3
4 to 6	122	42	80	65.6
6 to 8	42	19	23	54.8
8 to 10	16	11	5	31.3
10 to 15	7	4	3	42.9
Over 15	18	12	6	33.3
Total	1,350	329	1,021	75.6

1. A destruction of the natural diphtheria antitoxin content during an attack of poliomyelitis or of scarlet fever. In order to explain the greater prevalence of diphtheria among scarlet fever children, von Behring[2] and others have suggested that there is a temporary loss of the natural immunity to diphtheria during the acute febrile stage of the disease. This loss is caused, according to v. Behring, by a destruction of the small amount of natural antitoxin present in some individuals, which is just sufficient to give a negative Schick test. This destruction of the natural antibody content during an acute infectious disease has been claimed for measles as well as for scarlet fever. Karasawa and Schick,[3] however, have shown that in measles the natural antitoxin content in normal children, and later in the same children during an attack of measles, was approximately the same, thus demonstrating that there is no excessive destruction of antibodies against diphtheria during the febrile stage of measles. We had the opportunity of making an interesting observation bearing on this question in cases of scarlet fever and poliomyelitis. Some of the children suffering from these diseases, who gave a positive Schick test on admission to the hospital and were not immunized either actively or passively against diphtheria, continued to show a positive reaction during their entire stay in the institution, which varied from six to eight weeks. If the positive Schick reaction had indicated only a temporary loss of

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[2] Von Behring, E.: Ueber ein neues Diphtherieschutzmittel, Deutsch. med. Wchnschr., 1913, **39,** 873.

[3] Karasawa, M., and Schick, B.: Ueber den Gehalt des Serums diphtherie und masernkranker Kinder an Schutzkörper gegen Diphtherietoxin, Jahrb. f. Kinderh., 1910, **72,** 460.

the natural antitoxin during the febrile stage of the disease, then these antibodies would have rapidly reformed during convalescence and the retest with the Schick reaction would have been negative. The continued positive reaction rather points to the following possibility:

2. *A susceptibility to one of the less contagious diseases indicates that the child is also more apt to be susceptible to other contagious and infectious diseases.* From the little that is known of the infectiousness of poliomyelitis, we have in it a disease which is, according to Frost,[4] only one-fifteenth as infectious as scarlet fever. We would expect, therefore, that the relatively small proportion of children who are susceptible to poliomyelitis would be also more apt to be susceptible to diphtheria than children suffering either from scarlet fever or measles. Again, since scarlet fever is only about one-fourth as contagious as measles, we would also expect more scarlet fever than measles patients to be susceptible to diphtheria. In measles, on the other hand, we have, according to Herrman,[5] a disease which is almost universally contagious (96 per cent.) for children between the ages of 1 and 4 years. We would, therefore, expect to find in patients with measles the same, or only a slightly larger, number of children susceptible to diphtheria (positive Schick reactions), as in normal children. The four tables give rather strikingly corroborative proof of the probable correctness of this view.

These results do not, of course, explain the underlying and all-important question relating to the cause and nature of the so-called natural immunity. They lead, however, to the following suggestions:

1. Natural immunity can be best studied in a disease like diphtheria, for which we have a natural antibody that can be exactly measured in the animal test[6] and clinically determined by the Schick test.

2. The presence or absence of natural immunity, as shown by the Schick test, could be profitably studied in its relation to the Mendelian law. By making careful observations on a larger series of families, on the children as well as on their parents and possibly grandparents, some of the laws controlling the hereditary character of natural immunity might be revealed. To avoid errors, a history of diphtheria, or the recent administration of antitoxin, should always be carefully inquired into and noted with each individual.

We drew attention in our very first communication[7] to the fact that there is a probable hereditary element in the natural immunity against diphtheria. By natural immunity is not meant the short immunity present during the first few months of an infant's life. This immunity is only a temporary passive protection caused by the presence of antitoxic antibodies which are probably derived through the placenta from the mother's circulating blood. We pointed out that there is a distinct relationship and grouping among children belonging to the same family: (a) that the Schick test applied to the children in one family would be frequently either uniformly positive or negative in all; (b) where variations existed in the test, the older children generally gave the negative, the younger ones the positive reaction; (c) where the youngest child, if more than 2 years old, gave a negative Schick test, then the older children generally also showed a negative test. This interesting phenomenon, of course, pointed either to living under the same conditions of environment and the development of an immunity due to similar exposures, or else to an inherited family tendency to acquire early in life a natural immunity. This latter view is probably corroborated by the following observation: (d) Where the oldest child in a family gave a positive reaction, the younger children, with very few exceptions, also gave positive Schick reactions. It is difficult to conceive that in these families some of the older children had not been exposed, and probably frequently exposed, to infections with the Klebs-Loeffler bacillus. This can, therefore, only be explained by the absence of an inherited ability to develop an early immunity to diphtheria.

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[4] Frost, W. H.: Epidemic Poliomyelitis. What Is Known of Its Cause and Modes of Transmission, Pub. Health Rep., 1916, **31,** No. 28.

[5] Herrman, C.: The Communicability of Acute Poliomyelitis; Its Spread and Control, Am. Med., 1916, **11,** 713.

[6] Zingher, A.: A Modification of Roemer's Intracutaneous Method for the Determination of Small Amounts of Diphtheria Antitoxin in Blood Sera, Jour. Infect. Dis., 1916, **19,** 557.

[7] Park, W. H., Zingher, Abraham, and Serota, Harry M.: The Schick Reaction and Its Practical Applications, Arch. Pediat., 1914, **31,** 481.

SUMMARY AND CONCLUSIONS

1. The Schick test is positive between 1 and 4 years of age in about 32 per cent. of normal children, in a slightly larger proportion of cases of measles, in twice as many cases of scarlet fever and nearly three times as many cases of poliomyelitis.

2. Susceptibility to one of the less contagious diseases, like poliomyelitis, indicates that the child is more apt to be susceptible to other contagious and infectious diseases.

3. Natural immunity reveals interesting problems, which can be partly solved by a study with the Schick test in diphtheria immunity.

4. A uniform technic of making the test, standard solutions of toxin, a uniform interpretation of the test, and a large series of cases are essential in any attempt at making important deductions from the results obtained with the Schick reaction.

CLINICAL DEPARTMENT

A CASE OF DIAPHRAGMATIC HERNIA *

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History.—Baby G., 3½ months old, came under my care Oct. 6, 1916, with a history of recurrent attacks characterized by extreme cyanosis, dyspnea, and, judging from his hard crying, severe pain, the condition being relieved by a movement of the bowels or by the expulsion of gas, sometimes in large quantities.

His birth history was unimportant, and for two weeks he seemed a normal baby. The attacks were then first noted, and gradually increased in severity and frequency, until, of late, dyspnea had been more or less persistent, with several daily exacerbations of symptoms. The present attack had continued some forty-eight hours, with but little remission, and was the worst yet experienced.

Examination.—Examination showed a well developed, moderately well-nourished boy baby. He appeared practically moribund, being cold and cyanotic, and evidently suffering most extreme respiratory embarassment, there being violent recession of the lower chest wall at each inspiratory effort, with but little apparent intake of air, as though there were a laryngeal or tracheal obstruction. The throat was clear. On percussion of the chest, the left side gave a curious impression of hollowness, not exactly tympanitic in quality. The heart was found far over on the right side, and its action was very labored. Breath sounds were audible only over the upper portion of the right chest, none being heard on the left. The abdomen was much retracted.

Stimulation and the free administration of oxygen revived the baby, and a roentgenogram was taken, showing the presence of gas in the left side of the thorax (Fig. 1).

A diagnosis was made of probable diaphragmatic hernia, and this was confirmed by a roentgenogram taken after a barium enema (Fig. 2), in which the colon is seen within the chest cavity.

To determine the extent of the hernia, a barium meal was given and serial roentgenograms taken (Figs. 3 to 8), showing almost all the intestine above the diaphragm.

By more or less constant administration of oxygen, and routine washing out of the bowel, the baby was kept fairly comfortable for several days, but in view of the condition disclosed by the roentgenograms, it was manifestly impracticable to continue this treatment indefinitely.

It was therefore decided to open the abdomen on the bare possibility that an operable condition might be found, and this was done by Dr. L. P. Adams, October 13.

Operation.—The defect in the diaphragm was found to be an oblique slit about 1 inch long between the muscle fibers close to the point of penetration of the great vessels and esophagus. Through this the intestine was withdrawn and replaced in the abdomen, and the defect readily closed by sutures. The baby, however, survived the operation only a few hours.

COMMENT: A physician who had seen the baby from birth, and who had last examined it some two weeks before it came under my

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* Submitted for publication Dec. 10, 1916.

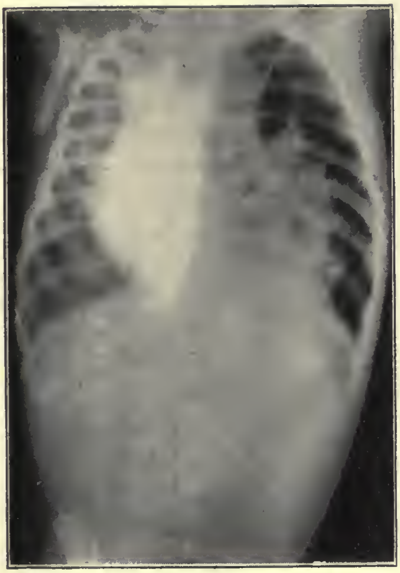

Figure 1

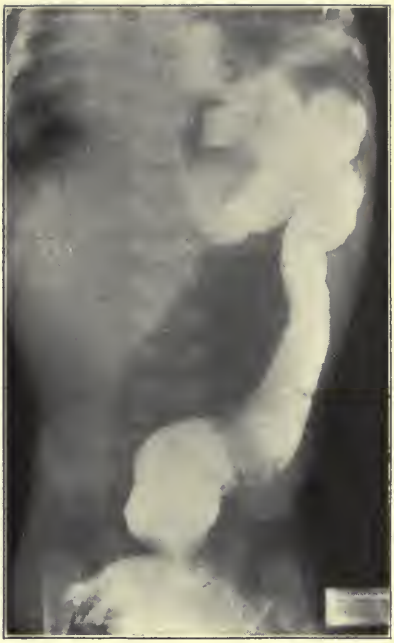

Figure 2

Fig. 1.—Author's case of diaphragmatic hernia, showing the presence of gas in the left side of the thorax.

Fig. 2.—Roentgenogram taken after barium enema, showing the colon within the chest cavity.

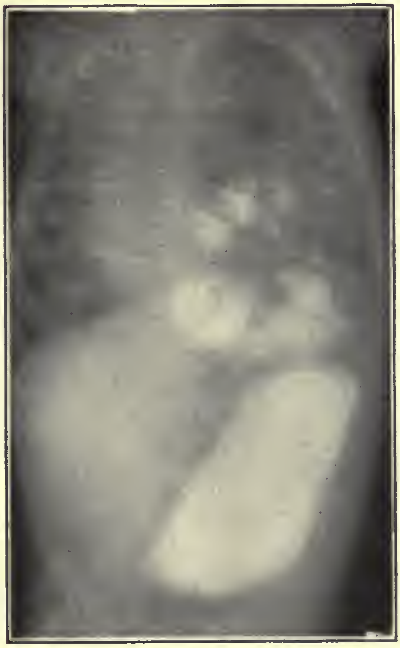

Figure 3

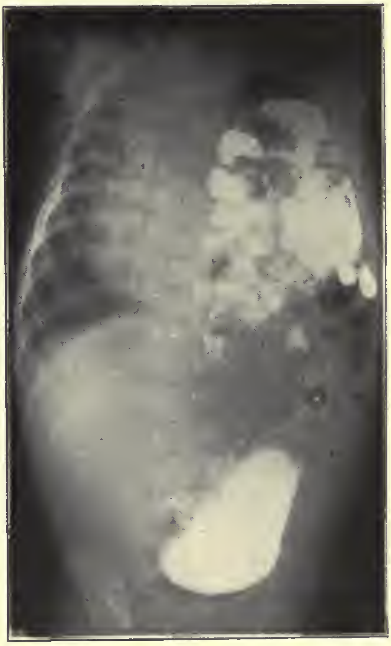

Figure 4

Fig. 3.—Roentgenogram taken fifteen minutes after barium meal, showing almost all of the intestine above the diaphragm.

Fig. 4.—Taken one hour after barium meal.

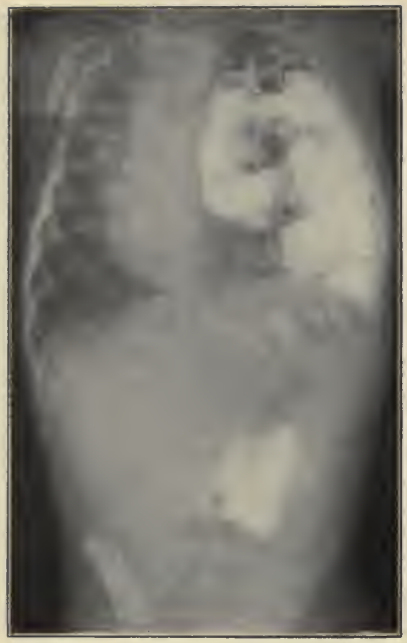

Figure 5

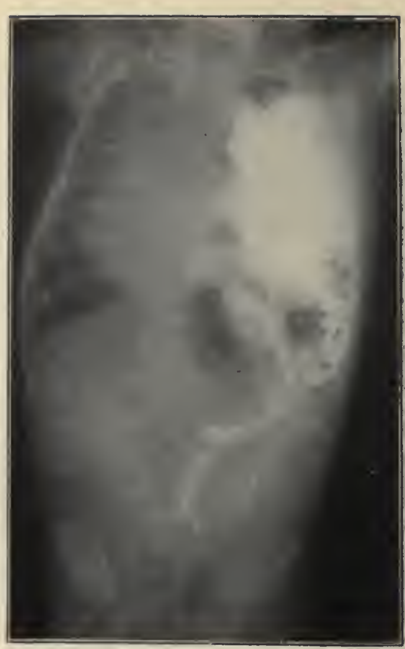

Figure 6

Fig. 5.—Taken two hours after barium meal.
Fig. 6.—Taken three hours after barium meal.

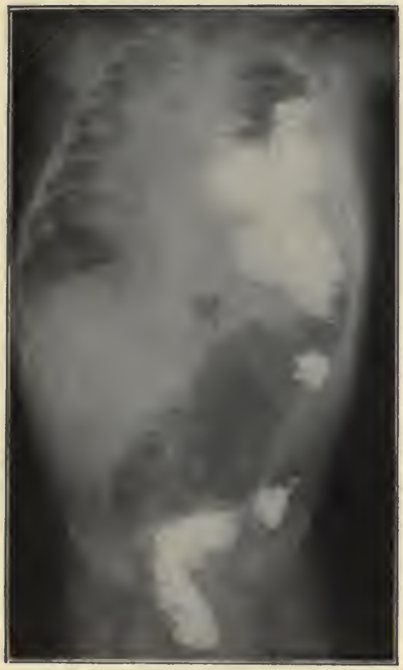

Figure 7

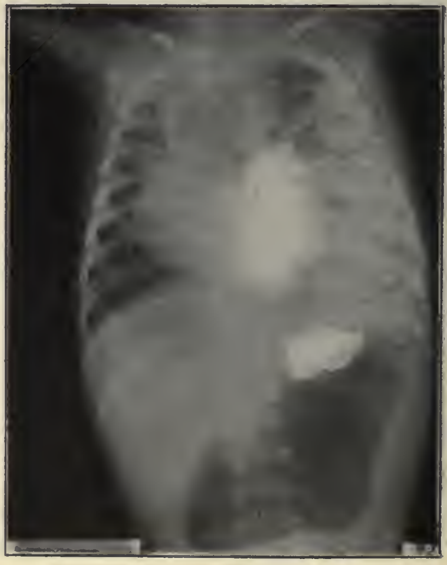

Figure 8

Fig. 7.—Taken five hours after barium meal.
Fig. 8.—Taken eight hours after barium meal.

observation, declared that he did not then or previously note the cardiac displacement and absence of breath sounds, and he believed that these signs developed later. The history of gradual increase, with recent very marked exaggeration of symptoms would also indicate that the herniation of the bowel into the thorax had been progressive. The defect itself, as disclosed at operation, was readily amenable to surgery, but the necessary handling, inch by inch, of the entire intestine at this time produced a degree of shock which could not be tolerated by an infant already weakened and worn out by many weeks of precarious struggle for breath. Had there been but little intestine to handle, as would have been the case in early operation, there would have been reasonable expectation of recovery.

A history of dyspnea and cyanosis, otherwise unaccounted for, especially if relieved by the passage of gas and feces, should excite suspicion of diaphragmatic hernia, and Roentgen-ray examination should be promptly resorted to, since this affords so ready and definite a means of diagnosis. This case demonstrates that the degree of herniation of the bowel is no criterion of the extent of the defect in the diaphragm, and would seem to suggest the propriety of early operation in all such cases.

I am indebted to Mr. P. L. Ansel for the excellent Roentgen-ray plates.

Federal Realty Building.

PROGRESS IN PEDIATRICS

RÉSUMÉ OF WORK ON TUBERCULOSIS IN CHILDREN FOR 1916

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MODES OF INFECTION

1. Von Weller, C.: Two Additional Cases of Miliary Tuberculosis of the Placenta with Clinically Latent Tuberculosis of the Mother, Arch. Int. Med., 1916, **17,** 509.

2. Ravenel, M. P.: Present Views in Respect to Modes and Periods of Infection in Tuberculosis, Jour. Am. Med. Assn., 1916, **66,** 613.

C. von Weller[1] reports two cases of miliary tuberculosis of the placenta, with clinical latent tuberculosis of the mother. He calls attention to the fact that the reported cases of placental tuberculosis may be arranged in three groups.

1. Cases in which the mother was known to be tuberculous and in which, as a result of this knowledge, the placenta was given intensive study and found to exhibit the characteristic lesions of tuberculosis, either with or without a demonstration of the bacilli.

2. Cases in which the mother was known to be tuberculous, and in which the presence of tubercle bacilli in the placenta or fetal blood was demonstrated by staining methods or by animal inoculation without the recognition of tuberculosis of the placenta.

3. Cases in which the maternal tuberculosis was clinically unrecognizable and in which characteristic histopathologic lesions of tuberculosis were found in the routine examination of placentas. In this group fall the two cases forming the subject of this report, also one other case previously reported by Dr. Warthin.

The first case was that of a woman of 21. On entrance to the obstetric service, April 23, 1914, no signs of pulmonary lesions were discovered, and on June 11 she was delivered of an apparently healthy child. The placenta was sent to the pathologic laboratory and in the course of the routine microscopic examination miliary tubercles were found. Eighteen months after the birth of the child both mother and child were under observation, were apparently well, and had given no evidence of tuberculosis at any time.

The second case was that of a woman of 27. She wilfully falsified in regard to her history in order to conceal an earlier diagnosis of tuberculosis. Examination revealed no signs of tuberculosis. She was delivered of an apparently healthy child Feb. 4, 1914. On routine examination of the placenta there was found a group of four or five miliary tubercles. The patient remained well for seventeen months after the birth of the child, except for some cough and sputum. She then developed well-marked signs of the disease.

That three such cases should be found in one laboratory and within the space of three years is strong argument, not alone for the belief that the maternal transmission of tuberculosis is much more common than is ordinarily thought, but also for the little recognized fact that a "subclinical" tuberculosis may be so influenced by pregnancy that the bacilli may enter the blood stream and produce placental or fetal miliary tuberculosis.

M. P. Ravenel[2] outlines the present views in respect to modes and periods of infection in tuberculosis. He says the evidence at hand indicates that in the majority of cases the respiratory tract is the route of infection. The work of Arnold and the experiments of Cornet are mentioned as furnishing the basis for this belief. Further evidence seemed to be at hand in the greater number of cases in which the supposedly primary lesion was found in the lungs and bronchial lymph glands as compared with the intestine and mesenteric glands. The value of this evidence, however, has been weakened during recent years by the discovery of the fact that in children the bronchial lymph nodes are often tuberculous, when no changes can be found in the lung; and the belief is growing that the lymph glands are first infected and the lung tissue involved later. Ravenel thinks, moreover, that the fixing of the portal of entry by the so-called oldest lesion is open to serious question. He has produced fatal pulmonary tuberculosis in monkeys by feeding tubercle bacilli. The oldest lesions were in the lungs and bronchial glands, yet the method of feeding precluded the possibility of the tubercle bacilli reaching the lungs except through the digestive tract. Practically all observers agree that in children there is a marked tendency to rapid and general dissemination of the disease, and many note that it is frequently impossible to determine the oldest lesion.

The alimentary tract is, according to Ravenel, a very frequent portal of entry for the tubercle bacillus, especially in children. The tubercle bacillus is able to pass through the intact mucous membrane of the alimentary tract without producing a lesion at the point of entrance. This takes place most readily during the digestion of fats. The bacilli pass with the chyle through the lacteals and thoracic duct into the blood, which conveys them to the lungs, where they are retained largely by the filtering action of the tissues.

The frequency of infection through the tonsil has been recently called in question by von Pirquet, and the evidence that the tonsils are often the portal of entry for the tubercle bacilli appears to the writer very conclusive, while it seems equally certain that food is the bearer of the infection in a large proportion of cases.

Infancy and childhood are preeminently the periods of life when the individual is susceptible to tuberculous infection, and infection occurs chiefly during these early years. Tuberculous infection in adult life occurs, but not so frequently or readily as is generally believed. A campaign against tuberculosis which leaves out of consideration the protection of children against infection will fail.

BACTERIOLOGY

3. Eastwood, A., and Griffith, F.: The Characteristics of the Tubercle Bacillus in Human Bone and Joint Tuberculosis, Jour. Hyg., 1916, **15,** 257.
4. Marfan, A. B.: Pathogenic Micro-organisms in Milk, Le Nourrisson, 1916, **4,** 34.
5. Beattie, J. M., and Lewis, F. C.: Successful Destruction of Tubercle Bacilli in Milk by Electricity, Brit. Jour. Tuberc., 1916, **10,** 23.
6. Beattie, J. M., and Lewis, F. C.: Successful Destruction of Tubercle Bacilli in Milk by Electricity, Jour. State Med., 1916, **24,** 174.

A. Eastwood and F. Griffith[3] have studied the bacteriology in 261 cases of bone and joint tuberculosis. Material used in their investigation was removed directly from an affected joint or bone, or from an abscess in the neighborhood of such a lesion. The bacilli isolated were described as the bovine or human type, or as atypical. From the 261 cases the human bacillus was isolated in 196 instances, the bovine in fifty-five, and the atypical forms in ten. In studying the age incidence of those infected by the bovine type, the authors found that in 155 cases of children under 10 years of age, forty-five, or 29 per cent., showed the bovine type of bacillus; in 106 cases of children over 10, only ten, or 9 per cent., showed the bovine type, and among forty-four over 16 years there were only three cases of bovine type.

In regard to the possibility of tubercle bacilli occurring in milk, A. B. Marfan[4] says that only exceptionally have they been found in human milk. A few experimenters have produced tuberculosis in animals by injecting them with the milk of tuberculous women. Marfan says that there are only two authentic reports of infants being infected by the milk of the mother. These were cases of Demme and Roger and Garnier. It is, however, necessary to interdict breast-feeding by all women afflicted with pulmonary tuberculosis. On the one hand, nursing lowers the mother's nutrition, and, on the other, the child receives an insufficient amount of milk, charged with toxic products, although it may not contain virulent bacilli. Moreover, a child nursing from a tuberculous mother runs the risk of being contaminated by the sputum, because of the intimate relation between nurse and babe.

Certain facts have been well established in regard to the transmission of tubercle bacilli by cow's milk. It has been demonstrated that cow's milk often contains living and virulent tubercle bacilli. In the milk of cows afflicted with mammary tuberculosis these bacilli are very abundant, and, contrary to what has been admitted previously, milk of cows, healthy in appearance and not presenting appreciable clinical evidence of disease of the mammary gland, may also contain virulent bacilli. This is true of the milk of any animal which has reacted to an injection of tuberculin. Virulent bacilli are also present in milk products, cheese, cream, and butter, and it seems that butter, considered less dangerous than milk, is often richer in virulent bacilli.

Milk may become infected by bacillary excrements after being milked. The fecal matter of tuberculous animals is often rich in bacilli; excrements soil the walls of the stables, the bed, and external parts of the animals, the hands of the milkers; dried, they penetrate the atmosphere and are scattered broadcast.

Milk infected with the tubercle bacillus may cause cervical adenitis in children, but more often tuberculosis of the mesenteric glands. The frequency of alimentary tuberculosis in the first years of life, then, can give an approximate idea of the frequency of infection from milk. Statistics extending over fifteen years have shown that alimentary tuberculosis occurs in children, especially from 2 to 5 years of age, and that it comprises 8 per cent., of all cases of tuberculosis observed. Today this proportion has diminished, notably because of better oversight of infected animals and of the general use of sterilized milk.

Marfan summarizes his paper as follows: As cows are often tuberculous, and, when they are, their milk is infectious, and as the ingestion of infectious milk can produce disease not only in animals but also in human beings, especially among the young, means must be taken to prevent this mode of infection. At present the boiling of milk seems to be the most practical preventive measure.

J. M. Beattie and F. C. Lewis,[5] completing a series of experiments on the treatment of tuberculous milk with electricity, think they have fully established the claims that this is efficient for the total destruction of the bacillus of tuberculosis in a milk supply. Injection into guinea-pigs of naturally occurring tuberculous milk, and of artificially infected milk, proved that the bacilli had been destroyed.

While in a later article the writers[6] say that more recent experiments would at first sight seem to suggest that the method is not wholly dependable, they conclude as follows: "Experiment seems to confirm our former opinion that this plan can be worked successfully, but there must be strict adherence to certain definite conditions of measurement, rate of flow, current density, etc., and further experiments are necessary to establish the relation of these conditions to one another."

SYMPTOMATOLOGY

7. Combe: Clinical Forms of Tuberculosis in Childhood, Le Nourrisson, 1916, **4,** 73.

8. Combe: Generalized Forms of Tuberculosis in Infants, Le Nourrisson, 1916, **4,** 155.

9. Koch, H.: Tuberculosis in Infancy, Ergebn. d. inn. Med. u. Kinderh., 1915, **14,** 99.

10. Wessler, H., and Bass, M. H.: Recurrent Hilus Infiltration, Am. Jour. Dis. Child., 1916, **11,** 198.

11. Aine, E.: Ulcerative Pulmonary Tuberculosis in Infants, Progrès. méd., 1916, **32,** 34.

12. Northrup, W. P.: Disseminated Miliary Tuberculosis, Arch. Pediat., 1915, **32,** 887.

13. Moore, J.: Acute General Tuberculosis with Left Oculomotor Paralysis after Measles, Dublin Jour. Med. Sc., 1916, **3,** 174.

14. Morse, J. L.: D'Espines Sign in Childhood, Am. Jour. Dis. Child., 1916, **11,** 276.

15. Reuben, M. S.: Fever: Initial Sign of Tuberculosis. Report of Cases, Arch. Pediat., 1916, **33,** 171.

16. Kleinschmidt, H.: Is There an Initial Fever in Tuberculosis? Monatsch. f. Kinderh., 1915, **13,** 513.

17. Adriance, V.: Tuberculous Infection in Infancy and Childhood, Boston Med. and Surg. Jour., 1916, **175,** 215.

18. Jeanneret, L.: Digestive Disturbance in Tuberculosis of Infancy, Arch. de méd. d. enfants, 1916, **19,** 29.

19. Morgan, E. A.: A Study of the Blood in Tuberculous Meningitis, Am. Jour. Dis. Child., 1916, **11,** 224.

20. Morquio, L.: Tuberculous Meningitis with an Increase in the Polynuclear Cells in the Spinal Fluid, Abstr. Arch. de méd. d. enfants, 1916, **19,** 218.

21. Ferdinando: Recovery from Tuberculous Meningitis, Abstr. Arch. de méd. d. enfants, 1916, **19,** 498.

22. Fiore, G.: Recovery from Tuberculous Meningitis, Abstr. Brit. Jour. Child. Dis., 1916, **13,** 348.

23. Jaquerod: Clinical Relations Between Erythema Nodosum and Tuberculosis, Rev. méd. de la Suisse romande, 1916, **36,** 345.

24. Barber, H. W.: A Case of Lichenoid and Nodular Tuberculide, Brit. Jour. Child. Dis., 1916, **13,** 148.

25. Little, G.: Acute Disseminated Tuberculosis Cutis, Brit. Jour. Child. Dis., 1916, **13,** 305.

26. Little, G.: Lichen Scrofulosorum, Brit. Jour. Child. Dis., 1916, **13,** 305.

27. McKenzie, D.: Atrophic Rhinitis and Tuberculosis, Jour. Laryngol., Rhinol. and Otol., 1916, **31,** 177.

Combe[7] divides the clinical forms of tuberculosis into two groups. In the first group he places localized, and in the second generalized forms. Of the localized forms, he distinguishes, (1) larval tuberculosis, (2) suspected tuberculosis, (3) tuberculosis masked as dyspepsia, (4) tuberculosis masked as anemia.

The only manifestation of the larval form is a positive Mantoux reaction detected in the routine examination of infants for causes other than tuberculosis. Radioscopic examination of the chest then reveals shadows indicative of enlarged tracheobronchial glands, and careful physical examination, areas of dulness or modified respiratory or voice sounds.

In the suspected form the infants have a tuberculous heredity and are below normal in weight and appearance. The Roentgen ray shows a more or less suspicious shadow. The von Pirquet or the Mantoux test is at first negative but, if repeated every fifteen days, it becomes positive.

The masked forms are the most important and are the result of the action of the tuberculotoxins. According to some writers, and Combe agrees with them, the tuberculotoxins act on the nervous system of infants, as of older children, and cause a decided change of character. The infant loses its gayety; it never smiles, but cries without cause. It sleeps badly, awaking often, but is difficult to arouse in the morning. The two characteristic effects of the tuberculotoxins, however, are the destructive action on the digestive ferments and the hemolytic action, giving rise to the dyspeptic and anemic forms of tuberculosis.

Combe found that in 85 per cent. of older tuberculous children the tuberculotoxins acted on the gastric glands and caused a lessened secretion of pepsin and hydrochloric acid. In infants this destructive action appears even more general and gives rise to a dyspepsia and consequent atrophy. In the dyspeptic stage the child is pale and emaciated, has slight appetite, and at the end of the meal regurgitates the food. Colic is a frequent symptom, the abdomen is tense because of gas, the stools are pale yellow, sometimes contain mucus, are acid in reaction, and have an odor of butyric acid. The infant is cross, restless, sleeps badly and has a slight fever.

In the atrophic stage, the emaciation is extreme. The child has the features of a little old man, with wrinkled, yellow, dry skin and thin extremities. In grave cases this appearance is accompanied by a hypothermia, irregular respiration, and concentration of the blood, shown by an increase in the number of red blood cells (6,000,000) and hemoglobin (150 to 160 per cent.). These symptoms of the dyspeptic and atrophic form do not differ essentially from the symptoms of other organic dyspepsias and atrophies, but careful examination often reveals other signs of tuberculosis, such as "facies vasodilatation," micropolyadenitis, macropolyadenitis, and hypertrophy of the spleen and liver. Of these the most important is the macropolyadenitis, which is characterized by the presence of many glands, the size of a pea or nut, in the subclavicular spaces, in the thoracic wall or in the abdominal wall, glands communicating with the pleura or peritoneum and having the same diagnostic significance for tuberculosis which enlargement of the epitrochlear glands has for syphilis. In order to establish a positive diagnosis of tuberculosis, however, all these signs must be confirmed by local signs of tracheobronchial adenopathy and by the Mantoux tuberculin test.

The form masked as anemia is more rare than the preceding, and gives rise to three clinical pictures: (1) that of a simple anemia, with a moderate diminution of red blood cells and hemoglobin and no microscopical changes; (2) that of an anemia pseudoleukemia, with diminution in the number of red blood cells and hemoglobin and disturbance in the hemolytic function of the bone marrow, which causes the blood stream to be flooded with red blood cells of all ages, normoblasts, macrocytes, myelocytes and myeloblasts; (3) the picture of a pernicious anemia, with considerable diminution of the red blood cells and a marked diminution in the percentage of hemoglobin, and a color index of plus one. The microscopic examination of the blood shows an almost normal condition, except for the large number of macrocytes and gigantoblasts. The appearance of infants with the masked anemia differs little from those with essential anemias. The chief difference is the redness of the lips, due to vasodilatation, in striking contrast to the pallor of the face.

These evidences of tuberculosis lead to a search for tracheoadenopathy by physical examination and roentgenoscopy. Prevertebral signs of enlarged glands, as dilated veins over the vertebrae, spinalgia, exaggerated voice and breath sounds heard below the fourth dorsal vertebra, and prevertebral dulness, are of questionable value in infants, and in any case can be relied on only when very apparent. Intervertebroscapular signs are more important. Thoracic vibrations are clearly increased in the lateral vertebral regions, if there is a mass of glands to transmit the sounds. Dulness in this region is a salient sign. A vesicular murmur on one side and bronchovesicular or bronchial murmur on the other are very conclusive. A diminution of the respiration on the same side as the dulness and bronchovesicular breathing indicate a compression of the bronchus by enlarged glands. However, as in the prevertebral signs, these must be very apparent in order to have diagnostic value.

Roentgenoscopy has become the best means of detecting enlarged tracheobronchial glands in infants, but considerable experience is necessary to interpret properly a roentgenogram of the thorax.

Combe[8] classifies the generalized forms of tuberculosis according to the mode of extension of the disease. In the first group he places the forms resulting from extension through the lymphatics, in the second those from extension by means of the bronchi, and in the third those from extension by means of the blood vessels.

He describes two forms resulting from extension through the lymphatics, namely, generalized and localized glandular tuberculosis. In the generalized form there is an involvement of all the glands of the body. At necropsy, masses of glands are found surrounding the bronchi and in the mesentery, and large solitary tubercles in the spleen, liver and kidney, but no generalized tuberculous infiltration of the viscera. Clinically, there is present the condition which Combe has previously described as "athrepsia vasodilatation." There is also marked pallor, a peripheral micropolyadenitis, and enlarged liver and spleen. But most characteristic are the masses of palpable glands in the subclavicular spaces, in the abdomen and in the iliac fossae. The Roentgen ray shows a definite enlargement of the bronchial and hilus glands, examination of the blood a leukopenia and a lymphopenia.

The localized glandular forms Combe designates as "hilus tabes" and "tabes mesentericus." In the first stage of hilus tabes the tuberculous process remains limited to the tracheobronchial glands; in the second stage it extends beyond the capsule of the glands into the pulmonary parenchyma. Separate tuberculous foci fuse and involve large areas of lung into a homogeneous mass. Clinically, these masses give the impression of a tumor, and the author prefers the name of pulmonary tuberculoma to tuberculous pneumonia, as it better indicates their hard, firm, homogeneous character, with absence of softening, and as it explains more satisfactorily the physical signs, which are those of a tumor and not of a pneumonia.

From the tracheobronchial gland the tuberculous infiltration involves the gland surrounding the aorta and then extends to the mesenteric glands. The prevertebral glands become caseated and form a voluminous mass in front of the last dorsal vertebra, a second occurs in the ileocecal region, and a third surrounds the transverse colon. The clinical picture is that of a mildly progressive cachexia. The abdomen is distended, especially to the right, where, on careful palpation the enlarged glands can be made out. Rectal examination allows of a more accurate localization, and differentiates the glands from fecal masses. The child usually suffers from a diarrhea; the stools are soft and yellow and contain fat, the failure to absorb which explains the emaciation.

According to Combe's experience, generalization of the tuberculous process takes place most frequently by aspiration of tuberculous material into the bronchi. Depending on whether the tuberculous material empties itself into the bronchi or bronchioles, there occurs an acute caseous pneumonia or an acute caseous bronchopneumonia. The symptoms of acute caseous pneumonia resemble those of a frank pneumonia which has lasted a long period of time. In the early stages the diagnosis may be made from the following: Examination of the blood shows an eosinophilia during the entire course instead of after the crisis, as in the frank pneumonias. The Mantoux reaction remains positive, while in the frank pneumonias it disappears during the febrile stage. The Roentgen ray shows a dense irregular shadow, not limited to the lobes, as it is in the frank pneumonias. Following the early or pneumonic stage is the stage of softening. The seventh day passes without a crisis, the condition remains grave, the fever seems of septic type, and the dyspnea continues. After a period of six or eight weeks, with remissions and exacerbations of the symptoms, the cough takes on the character of a whooping cough, and during an attack of coughing the child vomits a large amount of pus containing tubercle bacilli. Following these attacks of coughing there is a change in the physical findings. Instead of the bronchial souffle, many coarse râles, sometimes amphoric in character, are heard, and in the roentgenogram the dark pneumonic areas are replaced by shadows of cavities.

Caseous bronchopneumonia is one of the rarest forms of tuberculosis of infants. The tuberculous process starts at the hilus and gradually invades the lung, sometimes causing caseous infiltration of the periglandular tissue, sometimes forming numerous areas of caseous bronchopneumonia by aspiration of drops of pus into the bronchioles. These areas of caseous bronchopneumonia soften and empty themselves into the bronchioles and leave small cavities, "bronchopneumonic cavities"; also the peribronchial glands break down, forming a second group of cavities, "glandular cavities." The clinical picture is that of an ordinary bronchopneumonia with a very prolonged course.

The hematogenous forms of tuberculosis are rather frequent in infants. A softened gland opens into a blood vessel and a large number of tubercle bacilli are thrown into the circulation. If the rupture is into the pulmonary artery, a pulmonary miliary tuberculosis results; if into the pulmonary vein, a generalized miliary tuberculosis. An infant affected with acute pulmonary miliary tuberculosis presents all the signs of a febrile capillary bronchitis. The child is seized more or less suddenly with a constant cough, which nothing can alleviate, and which is accompanied with intense dyspnea and cyanosis. Somnolence alternates with restlessness. Examination of the lungs shows no definite signs of localization, but both lungs are filled with all varieties of râles. If the infant is already known to have a tuberculosis, the diagnosis of miliary pulmonary tuberculosis is not difficult, but if the child is seen for the first time, diagnosis is very difficult, especially as the Mantoux reaction is negative. The Roentgen ray, however, is of great help and shows a shadow having the appearance of granite or marble pathognomonic of miliary pulmonary tuberculosis.

Generalized miliary tuberculosis may be acute or subacute. In the acute form prodromal symptoms are exceptional, but, when they exist, they last weeks. These are anorexia, emaciation, cough, a change in disposition, and fever. The onset is sometimes sudden, marked by the appearance of fever, often accompanied by vomiting and diarrhea. Sometimes the onset resembles that of influenza (grippe) or the period of invasion of measles. General symptoms often entirely mask local symptoms and the clinical picture is that of typhoid. On the part of the respiratory system the symptoms are the same as those of a pulmonary miliary tuberculosis, and the Roentgen ray shows the same findings. The abdominal symptoms are anorexia, vomiting and diarrhea. The abdomen is distended, in spite of the cerebral involvement, which is an important evidence of miliary tuberculosis of the peritoneum. Symptoms on the part of the nervous system are pronounced. The child is at first cross and irritable, then somnolent; the fontanel is distended; there is hyperesthesia and finally rigidity and convulsions. Ptosis, inequality of pupils, strabismus, and conjugate deviation of the eyes and head are usually found. Examination of the urine usually shows albumin.

Subacute generalized tuberculosis is an attenuated form. At first the symptoms are those of a gastric fever, but after several months, cough and prostration appear and finally all symptoms of an acute miliary tuberculosis. Necropsy shows, besides the tubercles of recent date, older tubercles in nearly all the organs, and these cause the symptoms falsely attributed to gastritis.

Under the terms localized miliary tuberculosis, Combe describes the so-called surgical forms of tuberculosis. There are usually metastatic lesions from a tuberculous endarteritis, occurring in connection with tuberculosis of the tracheobronchial glands. The osseous form is relatively frequent in infancy and occurs as an osteomyelitis, affecting usually the phalanges (spina ventosa), or as tuberculous caries of the short bones, affecting usually the vertebrae, more rarely as tuberculous gumma of the flat bones of the skull. Tuberculous arthritis, osteoarthritis, and synovitis are more frequent in young children than in infants, although they do occur at this age. Cutaneous tuberculosis is a frequent metastatic occurrence. The lesions are usually the papulosquamous, the papulonecrotic, or more rarely the gummous tuberculids, the so-called scrofulodermata of the German writers.

After the study of 133 cases, H. Koch[9] gives a description of tuberculosis in infancy. He recognizes five forms, according to the portal of entry: the bronchogenous, the placentogenous, the enterogenous, the stomatogenous, and the dermotogenous.

Of the first, the bronchogenous, Koch has gleaned some very decisive facts from the history of his cases as to the source of infection, for in fifty he definitely determined this. In twenty it was the father, in twenty-seven the mother, in one both parents, in one the grandparent, in one a brother, and in one a nurse. Less definite was the information regarding the time of infection, but in most instances it was surmised to be very early. In Koch's experience the infected infants lived from three to twelve months, regardless whether the baby was breast or artificially fed. Infants infected from the mother, however, succumbed earlier than those infected from the father, for the reason, Koch thinks, that the infection from the mother through more intimate contact occurred at an earlier period.

Koch agrees with Kuesz, Albrecht and Ghon, that the primary infection takes place in the lungs and then spreads through the lymphatics. He is not quite in accord with the division into stage of incubation, of primary, and of secondary lesion, and with the conception that tuberculosis, lues and other infections are identical. But, if this division is adhered to, he regards the incubation stage from the time of infection until the tuberculin test becomes positive. The stage of primary lesion is that of the development of the lesion at the point of infection. This stage ends when the process spreads to the regional lymph glands.

Knowledge of the primary lesion is based on necropsy findings. It is impossible for the clinician, because of its inaccessible position, to make a diagnosis of a primary lesion. Its presence can be suspected by a positive tuberculin test, and sometimes it can be seen in Roentgen-ray plates. The material used by the author in the study of the primary lesion is the same as described by Ghon in his monograph on "The Primary Pulmonary Lesion." In fifty-eight necropsy records, thirty-eight cases showed one primary lesion, eight showed two lesions, four three lesions, and one case four lesions. In the other eight cases widespread tuberculous changes involved the entire lobe in which the lesion occurred. The primary lesion varied in size from a pea to a child's fist, and was either a caseous nodule or a cavity. In only three cases was there any sign of healing. The right lower lobe was the most frequent location. It was either deep in the pulmonary tissue or subpleural. In the neighborhood of the subpleural lesion was frequently a pleuritic exudate.

Koch found the usual duration of the stage of incubation was six or seven weeks. Fever did not develop until late in this stage. There was no change in nutrition or in the blood picture. During the stage of primary lesion the temperature is periodically subnormal and never goes above 38 C. The chief symptom is the cough, and this occurred in seventeen of the thirty-five cases. In five cases there was pallor of the skin and mucous membranes and a normal blood picture. In three cases there was sweating.

Extension of the process in the lungs can take place by further development of the primary lesion. Sometimes the primary lesion is surrounded by tubercles, sometimes cavities form, and sometimes the entire lobe is transformed into a cheesy mass. There also occur isolated tuberculous lesions due to aspiration of material containing tubercle bacilli. These usually have the characteristics of a lobular pneumonia. Physical examination and the Roentgen ray are of considerable help in diagnosing this stage. Cough is the most important symptom. Any type of temperature may occur.

From the primary lesions the tuberculous process spreads to the regional lymphatic glands. They caseate and soften and may rupture into the trachea or into a bronchus. Healing is rare in infancy. The chief symptoms of this stage are the harsh cough and expiratory stridor.

Extension to the upper respiratory tract may take place from the infected sputum, and in Koch's series there was one case of laryngeal tuberculosis and nine of pharyngeal and tonsillar tuberculosis. Extension to the intestinal tract may be caused by the infant swallowing the sputum. This occurred in forty-seven, or 35 per cent. of the writer's cases. In thirty-eight cases there were ulcers in the small and large intestines, in three a tuberculous peritonitis, and in six a tuberculosis of the mesenteric glands. Only exceptionally did the tuberculous ulcers cause symptoms, but the peritonitis caused abdominal tenderness, meteorism and diarrhea.

Extension also takes place through the circulation system. In the writer's series this form of extension caused osseous tuberculosis in five cases, tuberculosis of the skin in forty-four cases, usually of the papulosquamous variety, tuberculosis of the testicle in two cases, a solitary tubercle of the brain in one case and of the kidney in one case. If a richly infected material gains access to the circulation, a miliary tuberculosis, usually ending in tuberculous meningitis, results. The clinical picture depends on the localization of the miliary tubercles. The onset of miliary tuberculosis is only occasionally recognized. The condition is always accompanied by fever, usually continuous, but at times intermittent or remittent in type; only exceptionally is it subnormal. Emaciation is characteristic and sometimes there is severe anemia. If there are many tubercles in the lungs, dyspnea and cyanosis out of proportion to the physical findings occur. Often there is edema of the face and extremities and enlargement of the liver and spleen. An unfavorable sign is the appearance of tuberculids. The duration in the author's cases was from three to six weeks. Tuberculous meningitis has usually a sudden onset with fever. The infant loses appetite and is somnolent. Then symptoms of brain irritation, as vomiting, convulsions, and headache, develop. During the course of the disease there is stiffness of the neck, Kernig's sign, and dermographia. The sensorium becomes cloudy, and motor disturbances, like paralysis, especially in the region of the facial nerve, develop. The tendon reflexes are increased, the abdomen is sunken. The course is rapid, never longer than three or four weeks.

As to the outcome of tuberculosis in infants, Koch says that although most infants less than a year old die of miliary tuberculosis, he agrees with other recent writers that the prognosis is not so hopeless as was once thought. The prognosis depends on the time and the severity of the infection.

Diagnosis is based on the cutaneous tuberculin test. A positive reaction not only shows infection but tuberculous disease, for it is known that every tuberculous process in infancy is active. Clinically, the diagnosis is based on the general and local symptoms already described. The Roentgen ray is important for diagnosis of tuberculosis in the chest.

Koch is not much in favor of the tuberculin treatment of tuberculosis in infants. He advocates breast feeding and careful nursing. Surgical measures are rarely considered, as osseous tuberculosis is not frequent. As a prophylactic measure, the importance of keeping infants away from sufferers from phthisis is emphasized.

After dealing so exhaustively with the bronchogenous form of tuberculosis, Koch discusses the rarer forms. He says infection through the placenta is possible and cites twenty authentic cases collected by Cornet. Infection occurs by passage of bacilli from the placenta into the fetal blood or by aspiration of infected amniotic fluid, this latter being really an instance of bronchogenous infection. Symptoms of placental tuberculosis are few. The infants are below weight at birth and do not thrive well. The temperature is irregular. In some cases there is marked pallor. There may occur tuberculids, multiple caries, or lesions in the lungs. Involvement of the abdominal organs, enlargement of the liver and spleen stand in the foreground of the picture. The diagnosis is based on the history, the marked involvement of the abdominal organs, the absence of symptoms on the part of the lungs, and the appearance of a positive tuberculin reaction in the sixth or seventh week of life.

Primary enterogenous and stomatogenous tuberculosis are very rare. In the author's series there were only four of the former and three of the latter. In two cases of the stomatogenous form the primary lesion was in the tonsil. Infection through the skin takes place only when there is an injury. The most frequent reported cases are those following circumcision.

H. Wessler and M. H. Bass[10] describe a form of tuberculosis in children which they call recurrent hilus infiltration. They believe that this form of tuberculosis is an extension from the lymph nodes and occurs frequently enough to warrant its incorporation as a clinical entity in the great group of tuberculous infections of the lungs. For a knowledge of its morphology, they say, we are indebted entirely to the Roentgen ray. The lesion occurs in the majority of cases on the right side, and its point of predilection is the lung in the immediate vicinity of the fissure between the upper and middle lobes. Beginning with its base at the hilus, where a dark shadow of tuberculous nodes is present, a fairly opaque shadow of homogeneous density extends outward into the lung for a considerable distance, gradually fading into the normal lung tissue. The resulting infiltration is triangular in shape, its apex near the axilla. Its lower margin is sharply limited by the interlobular fissure. The latter is evidently thickened and is the seat of pleurisy, as it can usually be seen extending quite to the axilla beyond the limits of the infiltrated area. The infiltration does not remain constant in size or appearance, and this is perhaps the most remarkable fact in regard to these cases. The Roentgen-ray examination made at intervals of a month may show at first a wide area of infiltration, and at a later examination, nothing may be left but the thickened interlobular fissure. Such a sequence of infiltration and normal lung may be repeated several times and justifies the appellation of "recurring hilus tuberculosis."

The authors have found that children in whom this typical hilus involvement has occurred are usually brought to the physician on account of general debility, loss of weight, slight cough, or night sweats. Physical examination of the chest is often negative, unless the process has involved a considerable mass of lung tissue. This is a point of the greatest importance, for it emphasizes the fact that in debilitated children, with a positive von Pirquet test, Roentgen-ray examination is imperative. When the lesion is extensive, slight dulness to the right of the sternum may be present and expiration may be prolonged, harsh and accompanied by a few fine râles. The clinical picture is, moreover, peculiar, in that it shows considerable variation in the same case at different times. There is apparently a recurrent inflammatory process, which, as it extends from the hilus into the lungs, produces an exacerbation of the clinical signs and symptoms. At such times there is more rapid emaciation, more weakness, more fever, and possibly more cough. It is during such exacerbations that the Roentgen ray reveals the extension into the lung as described above. In the favorable cases, and the majority seem to be of this type, there is a distinct regression, the symptoms all becoming milder and the Roentgen ray coincidently showing a diminution in the amount of lung involvement.

E. Aine[11] describes ulcerative pulmonary tuberculosis in infants. He says that it was not exceptional to encounter in autopsies on infants who had died of tuberculosis, more or less extensive ulcerative lesions, analogous to those which characterize pulmonary tuberculosis in the adult. Anatomically, these ulcerative lesions occur in four forms. In the simplest form there is a single tuberculous cavity, which apparently represents the primary focus of infection, and is most frequent in infants from 3 to 6 months old. The second and most common form consists of a cavity embedded in an area of caseous pneumonia. The cavity is large and multilocular, evidently the confluence of a number of smaller cavities primarily separated. The third form consists of small multiple cavities scattered through one lobe or one lung; they are always located around a bronchus and are due to breaking down of a caseous bronchopneumonia. In the fourth form the cavities are situated in the midst of dense fibrous tissue containing dilated bronchi. The author has observed that in all forms of ulcerative tuberculosis in infants the cavities are situated nearer the surface of the lung than in adults.

Cavity formation in infants gives rise to few clinical signs or symptoms, of which persistent dulness at the apex is most important; hemoptysis is of especial importance, but rarely occurs. Roentgenography is of great service in diagnosis.

W. P. Northrup[12] reports a case of disseminated miliary tuberculosis in a 15-months-old baby in whom the Roentgen ray proved a helpful diagnostic aid. The mother and one brother also had tuberculosis. The baby had been sick with wasting for one month before entering the hospital. Physical examination showed a poorly nourished infant, with discharging nose and enlarged glands. There was a papulopustular, umbilicated skin eruption, most abundant on the trunk, with a few lesions on the face and on the dorsal surface of the forearm. There was a pea-sized nodule in the subcutaneous tissue on the left forearm, one on the arm, one on each calf, symmetrically placed. One of these, removed and examined, proved to be tuberculous.

The physical signs in the chest were difficult to diagnose. The percussion note was unchanged, there was no bronchial voice or breathing, and no râles in front. At the angle of the scapula there were increased voice sounds and whistling râles. In a marantic infant these would not be conclusive, but the Roentgen ray helped to a diagnosis and showed a disseminated miliary tuberculosis of the lungs. In the absence of convincing chest finding and typical clinical tuberculous skin lesions, the Roentgen ray served here a most useful purpose.

J. Moore[13] reports a case of generalized tuberculosis with paralysis of the left oculomotor nerve which occurred after an attack of measles. The child had been well until the attack of measles a few weeks previously, and after that had bronchopneumonia. When she was admitted to the hospital the temperature was subnormal, and there was complete paralysis of the third nerve on the left side with dilatation of the pupil and inability to turn the eye inward and upward. There was also external strabismus and loss of power of accommodation and contraction to light. Ophthalmoscopic examination showed a choroiditis. The base of one lung was congested and the child had a cough.

On the basis of the subnormal temperature the author made a diagnosis of tuberculosis, which was substantiated by the future course of the disease. Objective evidence of lung trouble increased and the child's strength failed rapidly. She became at first listless, then semicomatose, and finally entirely unconscious. The abdomen had the scaphoid form so characteristic of tuberculous meningitis. Death occurred ten days after entrance.

Postmortem, there was found a disseminated tuberculosis of both lungs and of the mediastinal and peribronchial glands, pericardium, diaphragm, liver, kidneys, spleen, peritoneum, and of the basal meninges. No involvement could be made out of the nucleus or of the intracranial course of the third nerve either macroscopically or after hardening and examining sections.

J. L. Morse[14] has undertaken a study of D'Espine's sign, because of the difference of opinion which prevails as to what constitutes this sign, and because of his impression that it is much less frequent in the children of the well-to-do than in those of the hospital class, and, when present in the children of the well-to-do, it is in a considerable proportion of the cases not a manifestation of tuberculous infection. Six hundred and sixty-six patients seen in office and consultation practice form the basis of the study.

Both the whispered voice and the spoken voice were used in making the tests. In 626 of the 666 children, or 94 per cent., the change in voice sounds occurred between the seventh cervical and the first dorsal spine. These figures seem sufficient to prove that D'Espine's original contention as to the location of the normal change is correct.

The fact that this sign was present in but forty of 666 children, or only 6 per cent., shows that it is uncommon in the children of the better classes.

In eighteen, or nearly 50 per cent., of the children the enlargement causing D'Espine's sign was probably not tuberculous. In nine it probably was tuberculous, and in thirteen there were no data pointing one way or the other. These figures show what is now generally accepted, namely, that D'Espine was wrong in his conception that his sign was always a manifestation of tuberculosis of the bronchial glands. The presence of this sign means merely that there is some tissue between the trachea and bronchi and vertebral column which transmits the bronchial sound unchanged, whereas under normal conditions it is modified during transmission.

M. S. Reuben[15] discusses fever as the initial sign of tuberculous infection in children. He bases his conclusions on the study of infants coming to the milk station. In three instances the exact time of onset of the tuberculous infection was determined, as the children were under observation from early infancy. In each of these the mother was tuberculous. The cutaneous tuberculin reaction was performed on these infants once every month and found negative as long as the infant was gaining in weight and had no fever; with the onset of fever, however, a positive reaction was obtained in two of these cases, and in the third a positive reaction after the fever had lasted a week.

Reuben believes that fever is the first sign of tuberculous infection in infants. The fever is of sudden onset; at first is high and remittent in character, then gradually falls by lysis, but not to normal; it continues slightly above normal, 100 to 101 F. for twelve to twenty weeks, with periods of complete absence of fever. Exacerbations of high fever, of the same type as that of the onset, usually occur. The tuberculin reaction in these cases becomes positive at the onset of fever or within a few days. At first there are no physical signs, but these develop within the course of a few weeks. In patients who recover they gradually disappear. The prognosis of tuberculous infection in infancy is more favorable than was formerly supposed; 30 to 35 per cent. survive the infection.

Reuben also found that in infants 14 per cent. of prolonged febrile conditions diagnosed as influenza gave a positive von Pirquet reaction, and he thinks it possible that many other fevers of obscure origin may be due to tuberculous infection. He urges that a tuberculin test should be carried out on every infant who has an idiopathic fever and presents no physical signs.

H. Kleinschmidt[16] believes that the assumption of an initial fever in tuberculosis must be deferred until more data on the subject have been accumulated. He reports a case of an infant nursed by the mother who was suffering from tuberculosis in an advanced form and who died shortly after the child's birth. The child seemed to thrive on a simple milk mixture and had a temperature constantly normal. On the fifty-first day the von Pirquet test became positive and it was not until two weeks later that the child developed fever. Symptoms of generalized tuberculosis rapidly followed and the child died at the age of 3 months.

According to L. Jeanneret,[18] the frequency of digestive disturbances in the tuberculous child has long attracted the attention of pediatricians. He divides these disturbances into primary and secondary dyspepsias. The secondary form is due to overfeeding, and Combe was the first to draw attention to the numerous cases of enteritis due to superalimentation. Secondary dyspepsias are more frequent in private practice, where parents still have the false idea of the necessity of overfeeding and of giving much medicine. In the hospitals, where the régime is simple, this form is never observed.

Jeanneret has carefully gone over the histories of his tuberculous children and has found that 50 per cent. suffered from primary dyspepsia. Very often this digestive disturbance was the first symptom and led the parents to consult the physician. Primary dyspepsias in tuberculous children may be mild or severe. In some instances the patients present the picture of a chronic enteritis and always are seriously handicapped.

The author's treatment is as follows: As he found in thirty-five of 120 of his cases an anachlorhydria, he gives an amount of food proportionate to the quality of the digestive juice, which is ascertained by gastric analysis. He diminishes the kind of food which requires acid for digestion, but does not suppress meat entirely, since it is an excitant of gastric secretion. To supply the deficient secretion he gives a teaspoonful of the following mixture after each meal: 3 parts pepsin; 5 parts hydrochloric acid; 50 parts syrup of raspberry and water to 120 parts. Under this régime the digestive disturbances quickly disappear.

A lack of uniformity in the blood picture of tuberculous meningitis observed at the Babies' Hospital has led E. A. Morgan[19] to attempt establishing an average figure for the blood count in this condition. For this purpose 169 cases of tuberculous meningitis from the records of the hospital for the last eight years were analyzed. There were 252 counts made on the 169 cases.

The conclusions drawn were as follows: The leukocyte count in tuberculous meningitis is higher than has heretofore been described. The average in this series was 20,900 per c.mm. with 72.6 per cent. polymorphonuclears. The total leukocyte count and the proportion of polymorphonuclear cells vary with the stage of the disease; that is, both counts increase as the disease advances. There is a relative but not absolute diminution in the mononuclear elements of the blood. There is a definite relationship between the intensity of the tuberculin reaction, on the one hand, and the total leukocyte count and polynuclear percentage, on the other. Diminution in the intensity of the tuberculin reaction is accompanied by an increase in the total leukocyte count and polymorphonuclear percentage, both being evidence of a failing resistance of the body to the tuberculous infection.

L. Morquio[20] reports six cases of tuberculous meningitis in which the spinal fluid showed a polymorphonuclear leukocytosis. The first case was a 14-year-old girl who entered the hospital Sept. 14, 1910, with symptoms of meningitis. Lumbar puncture on the 24th gave a clear fluid with 310 cells to the c.mm., 53 per cent. of which were polymorphonuclears and 47 per cent. lymphocytes. On the 27th another puncture gave a slightly cloudy fluid, containing 780 cells to the c.mm., 47 per cent. of which were polymorphonuclears and 53 per cent. lymphocytes. The second case was an 11-year-old girl. In the spinal fluid were 50 per cent. polymorphonuclear cells and 50 per cent. lymphocytes. In the third case, a 6-year-old boy, the spinal fluid was slightly cloudy and showed 98 per cent. polymorphonuclear cells. In the fourth case, also a 6-year-old boy, the spinal fluid contained 80 per cent. polymorphonuclears and 20 per cent. lymphocytes. In the fifth case there were 62 per cent. polymorphonuclears and 38 per cent. lymphocytes, and in the sixth, 75 per cent. polymorphonuclears and 25 per cent. lymphocytes.

Ferdinando[21] reports a case of tuberculous meningitis followed by recovery. The patient was an 11-year-old girl with a family history of tuberculosis. She had been sick fifteen days with cough and irregular fever. Examination on entrance to hospital showed pallor, emaciation, and micropolyadenopathy. There was convergent strabismus, ptosis of the right eyelid, stiffness of the neck, Kernig's sign, spasmodic muscular movements, hyperesthesia and rough breathing over the lungs posteriorly. Lumbar puncture gave 40 c.c. of clear fluid containing lymphocytes and tubercle bacilli. After puncture all symptoms subsided and in about fifteen days the child was considered cured.

G. Fiore[22] adds the report of another case of recovery from tuberculous meningitis to the two others which he has previously reported. The third patient was an 8-year-old girl who had had convulsions when 1 month old. She was admitted to the hospital with signs of lymphatism, tracheobronchial adenitis and bronchopneumonia. The von Pirquet test was strongly positive. The bronchopneumonia cleared up, leaving only a patch of harsh breathing at the apex of the right lung. Shortly afterwards there developed vomiting, headache, drowsiness, irregular fever, increased reflexes, dermographia and cranial tympany on percussion. Lumbar puncture gave abundant clear fluid under pressure, which contained an increased number of lymphocytes and amount of albumin, and which produced tuberculosis in a guinea-pig. The patient's condition remained unchanged for a month, then began to improve, so that at the end of six months, recovery was complete. Lumbar puncture was practiced eight times and each time the pressure was less and the lymphocytes and albumin diminished.

Jaquerod[23] believes that there is a causal relation between tuberculosis and erythema nodosum and that the association of the two is not merely a coincidence. He reports two cases of erythema nodosum, one in a girl of 10, the other in a boy of 5, extremely severe but with rapid and apparently complete recovery. Both children had latent glandular tuberculosis and the eruption appeared after an acute gastritis in the former and an attack of influenza in the latter. Jaquerod thinks these intercurrent affections aroused the tubercle bacilli and produced a transient tuberculous toxemia, which in turn was responsible for the erythema. The prognosis is that of the tuberculous infection, and there is no reason to believe that those who develop erythema nodosum are more likely than those who do not, to have serious tuberculosis later. The author has had a number of patients with erythema nodosum who are now in robust health after periods ranging up to fifteen years.

H. W. Barber[24] reports a case of lichenoid and nodular tuberculid in a 4½-year-old boy. Following an attack of measles an eruption appeared, first on the hands and knees and then on the trunk. The lesions on the trunk were lichenoid and those on the hands and knees nodular. Physical examination of the chest revealed signs of enlarged bronchial glands.

Little[25] reports a case of lichen scrofulosorum in a 13-year-old girl who had been treated for two years with small doses of tuberculin in the form of bacillary emulsion, for scrofuloderma of the neck of five years' duration. Lichen scrofulosorum had recently appeared suddenly in the form of a large number of patches of grouped follicular papules, the patches forming oblong or circinate shapes, from 1 inch to 4 inches in diameter, and distributed on the front of the trunk, between the navel and the nipples, and on the back. The papules were of a vivid red, somewhat more salient and vivid in color at the periphery. The patches had persisted with little change except that there was a slow but progressive fading of color, due probably to the omission of the tuberculin injections.

The same writer[26] also reports a case of acute disseminated tuberculosis cutis in a male infant 7 months old, eruption having come out acutely about a fortnight before. The whole of the skin from the buttocks to the feet was closely covered with an eruption of small, deep bluish, nodular lesions, varying in size from 1/16 inch to ¼ inch. Above the level of the pubes the skin was unaffected. The cervical glands had become enlarged at the age of 2 months, and the mastoid had been operated on for tuberculous disease at the age of 3 months. After the removal of about twelve caseous glands, in which bacilli were easily found, the eruption faded considerably.

D. McKenzie[27] has undertaken a study to determine whether any relation except accidental existed between ozena and tuberculosis. He has ascertained the following facts: Tuberculosis was found in the majority of necropsies on ozenatous patients. Clinical examination revealed tuberculosis in 20 to 58 per cent. A family history was revealed in 46 to 90 per cent. The von Pirquet test was positive in 80 per cent. of the patients under 15 years of age, and the subcutaneous test in 94 per cent. From these observations McKenzie draws the following conclusions. There is evidence of the frequent association of tuberculosis and ozena, in the clinical examination, the family history, and in the result of the tuberculin tests. This evidence is supported by the results of tuberculin treatment. There is also evidence that the acid fast bacillus in the ozenatous crusts in an attenuated form of tubercle bacillus. Ozena in many details resembles other paratuberculous diseases.

DIAGNOSIS

28. Combe: Diagnosis of Tuberculosis in Infancy, Le Nourrisson, 1916, **4,** 1.
29. Smith, C. J., and Bibby, H. L.: Observations on Tuberculosis at the Vanderbilt Clinic, Arch. Pediat., 1916, **33,** 782.
30. Dunn, C. H.: Tuberculosis in Infancy, Am. Jour. Dis. Child., 1916, **11,** 85.
31. Sedgwick, J. P.: Diagnosis of Early Tuberculosis in Childhood, St. Paul Med. Jour., 1916, **18,** 213.
32. Zitronblatt, A. Y.: Skin Tuberculin Test in Surgical Tuberculosis, Russk. Vrach., 1915, **14,** 708.

Combe[28] bases the diagnosis of tuberculosis in infants on the following: 1, heredity; 2, the general appearance; 3, the Roentgen-ray examination; 4, bacteriologic tests; 5, tuberculin tests; 6, the clinical examination.

The author's statistics show a family history of tuberculosis in 90 per cent. of his cases, if in the word family is included all who live in intimate contact with the family. A careful detailed history is of great value in diagnosis, but must include not only father and mother, but brothers, sisters, servants; in fact, everyone closely associated with the child.

The appearance of the infant is most deceptive in regard to diagnosis of tuberculosis. On the one hand, a tuberculous infant may appear absolutely normal, while on the other, an infant with atrepsia or a chronic bronchopneumonia may be so cachectic that the diagnosis of tuberculosis seems certain. However, there exists a condition in the infant suffering from tuberculosis which Combe calls "facies vasodilatation," and which suggests at once further search for the disease. Infants with "facies dilatation" are cyanotic, they appear old for their age, they have long curly lashes, eyebrows and hair, bright eyes, over-red lips, and a hairy, moist skin. In the presence of this condition Combe suggests search for tuberculous lesions in the bones of the skull, the phalanges, and joints. Papulonecrotic tuberculids may be discovered on the trunk, shoulders or limbs, chronic tuberculous ulcerations in the skin, or masses of glands in the subclavicular or submaxillary regions. Or there may be a phlyctenular keratitis or chronic suppurative otitis media, with multiple perforations of the drum and formation of granulations, so characteristic of tuberculosis of the middle ear.

Examination with the Roentgen ray shows enlargement of the bronchial glands or areas of consolidation in the lungs. It does not, however, indicate whether the enlargement is the result of an influenza infection or a previous bronchopneumonia, or whether the pulmonary shadows are the remains of a fibrinous pneumonia or of an atelectasis. The radioscopic examination alone leads to an erroneous diagnosis. It must be interpreted and substantiated by clinical and biologic tests.

Bacteriologic examination allows of a positive diagnosis, but finding the tubercle bacillus is often difficult, as the sputum is usually swallowed. The author has, however, often been able to demonstrate tubercle bacilli in the vomitus or stomach washing or feces, or in the mucus obtained by swabbing out the pharynx.

Combe regards the Mantoux intradermal tuberculin reaction as more exact, more reliable and more sensitive than the von Pirquet test. For six years he has used the von Pirquet test on one arm and the Mantoux on the other and thus in many hundreds of infants has compared the value of the two tests. To perform the test, he injects into the skin of the arm $\frac{1}{10}$ mg. of old tuberculin. Combe describes four types of reactions. A normal reaction, in which in twenty-four hours there is the formation of a red papule of varying dimensions. The scrofulous reaction, in which the papule is more prominent and is surrounded by a painful area of redness 5 to 10 cm. in diameter. This reaction occurs in children with the exudative diathesis. In some instances the papule becomes capped with more or less numerous vesicles, which, on drying, leave a pigmentation. In other instances a pustule caps the papule, which, on healing, leaves a small scar. The value of this test depends on its proper performance and the correct interpretation of the reactions. The author believes that a positive reaction indicates that the infant has been infected with the tubercle bacillus, but does not indicate whether the resulting condition is a latent tuberculosis in evolution or a cured tuberculosis. A negative Mantoux reaction, on the other hand, does not exclude tuberculosis. In the first place, if the infection is recent, the infant may not have had time to produce sufficient antibodies to cause a reaction, and the test should be repeated every month for at least three months. In the second place, it is necessary that the organism be capable of forming antibodies. In profound cachexia and just before death this faculty is lost. In cases of miliary tuberculosis the antibodies are absorbed by the tuberculin already produced in the organism. A number of acute infections prevent the formation and cause the absorption of antibodies. A negative Mantoux reaction, then, is due to the absence of antibodies, not to the absence of a tuberculous infection.

The inspiratory and expiratory stridor, the harsh bitonal cough, and the spasmodic attacks of cough resembling whooping cough seem, according to the writer, to be most important symptoms. The inspiratory stridor, due to pressure of enlarged bronchial glands on the trachea, must be differentiated from the inspiratory stridor of laryngeal obstruction. In laryngeal stenosis the child throws its head backward, to open, as far as possible, the larynx; in tracheal stenosis the head is thrown forward. In laryngeal stenosis the voice is altered, while in tracheal stenosis it remains normal. In laryngeal stenosis the larynx descends during inspiration, in tracheal it remains stationary. The bitonal cough is due to the lack of symmetrical functioning of the vocal cords, so that the sound emitted by each differs in pitch. The attacks of spasmodic cough are differentiated from those of whooping cough by the absence of the crow at the end of expiration, by the fact that the attacks do not occur regularly and are not more frequent at night. The expiratory stridor is the most important sign, because it occurs early and is not found in any other condition. Inspiration is silent, but expiration is noisy and prolonged.

C. H. Smith and H. L. Bibby[29] report their observations at the Vanderbilt Clinic on tuberculosis in children. When a child was brought for examination, they asked two questions: (1) Has the child been infected with tuberculosis? (This question was answered by the skin test.) (2) Is the infection latent or active? Active and latent seem terms preferable to infection and disease, since they are more accurate, and since all infection means disease. An active tuberculosis in a child was not like an incipient tuberculosis in an adult. The diagnosis in the child was made on symptoms of impaired nutrition and anemia, undersize, and failure to gain in weight. The presence of fever lasting over a considerable length of time was suggestive. Other valuable symptoms were anorexia, fatigue, languor, headache, and night sweats. In children, cough and positive chest signs were rare, but there might be transient bronchitis, asthmatic bronchitis, and enlarged bronchial glands. The authors found physical signs in the lungs in only twenty-one of 150 cases. The physical signs were transient, localized râles at the apex in one case, localized râles in the axilla in three cases, generalized bronchitis in two cases, asthmatic bronchitis in five cases, pleurisy in four cases, consolidation with cavity formation in four cases. The signs of involvement of the bronchial glands were dulness, tender spine, and D'Espine's sign.

The writer thinks that the Roentgen-ray is of value only when a short exposure can be made. Enlarged bronchial glands or tracheal-bronchial involvement might give large central shadows or small nodes might give shadows along the bronchi.

C. H. Dunn[30] found in a series of sixty-two successive necropsies on children in the first two years of life that tuberculosis was considered the direct cause of death in twenty-three cases and the contributing cause in two. He therefore emphasizes the importance of tuberculosis in infancy.

In this series of necropsies Dunn investigated the question of primary lesion, and as a result, it was actually found at the portal of entry in twenty-two of the twenty-five cases. He believes with Ghon that, when a primary lesion is not found at the portal of entry, it is overlooked. The fact that the primary lesion was found in the lung in twenty cases and in the intestine in two cases suggests that in Boston at least the most frequent mode of infection is by inhalation of tubercle bacilli from a human source, but that infection through the ingestion of bovine bacilli in contaminated milk may occur.

The lesion found in the lung seemed quite easily recognizable as a primary lesion, and distinguishable from the widespread secondary lesions. In most cases it was a circular area, varying in size from that of a pea to that of a hazelnut. The center was caseous, but usually of a grayer color than the yellowish-white caseation seen in the secondary lesions. In some there was caseous softening or small cavities; in one there was calcification. In a few cases the primary lesion was much larger, reaching to the pleura, where its situation was marked by firm fibrous adhesions. Around the periphery of some of the smaller lesions were numerous miliary tubercles, suggesting direct extension. The favorite situations of the primary lesions were at the apex and near the hilus. The lesion found in the intestine and considered primary was a tuberculous ulceration.

The secondary lesions found in the lungs were of two distinct kinds. One was a tuberculous bronchopneumonia, characterized by exudate into the pulmonary alveoli, with more or less necrosis or caseation. The other secondary lesion was a miliary tuberculosis. The bovine type of bacillus was found in one case, and the human type in four.

A diagnosis of the tuberculous nature of the disease was made during life in twenty-three of the twenty-five cases, and was based on (1) the finding in the chest of physical signs which suggest tuberculosis; (2) the evidence given by the tuberculin test; (3) the evidence given by Roentgen-ray examination of the chest. Signs suggesting tuberculosis were found in fourteen of the twenty-five cases. In comparing the physical signs with the postmortem findings the following conclusions were drawn: 1. Acute miliary tuberculosis of the lung without tuberculous bronchopneumonia gives no recognizable signs in the lung. 2. Tuberculous bronchopneumonia usually does give signs; in some cases only scattered râles, in others signs of consolidation in various parts of the chest. 3. The presence of d'Espine's sign in infancy usually means tuberculosis of the bronchial lymph nodes, but the sign may possibly not be obtained, although the glands are found enlarged at necropsy. 4. The primary lesion gives no signs in the chest, unless very large, and in such cases the signs are only those of consolidation and are indistinguishable from tuberculous bronchopneumonia.

In testing the reaction to tuberculin only the von Pirquet test was employed. On the whole, the author is inclined to believe that the value of the cutaneous tuberculin reaction in infancy is not so great as many writers and statistical reports have inferred. A negative reaction seems to be a frequent finding in any stage of the disease and gives no evidence at all. A positive reaction, on the other hand, means tuberculosis.

Roentgen-ray examination of the chest was made in thirteen cases, and was positive in every case. In several cases it was the only positive finding. In general, there was a surprisingly close correspondence between the Roentgen-ray picture and postmortem findings. The enlargement of the bronchial lymph nodes could be made out in most cases. Tuberculous bronchopneumonia was correctly diagnosed in several cases, but not in all in which it was found postmortem. The primary lesion was not shown, when small, but was conspicuous when very large. Miliary tuberculosis of the lung without tuberculous bronchopneumonia was not shown.

PROGNOSIS

33. Combe: Prognosis of Tuberculosis in Infants, Le Nourrisson, 1916, **4,** 202.

34. Permin, G. E.: The Skin Tuberculin Test in the Prognosis of Tuberculosis in Young Children, Hospitalstidende, 1916, **59,** 697.

According to Combe,[33] the opinions of pediatricians differ as to the prognosis of tuberculosis in infants. While most declare that, when diagnosed clinically it is absolutely fatal, others affirm that they have seen infants survive tuberculous disease. Combe is of the opinion that the prognosis of tuberculosis in infants is very grave, but not inevitably fatal. He thinks the outcome depends on a number of factors. The age of the child at the time of infection is the first point to consider. The younger the child is at this time, the less capable he is of defending himself and the greater is the tendency of the tuberculosis to become generalized. The virulence of infection and the opportunity for reinfection are important factors. Contact with open tuberculosis offers this opportunity for reinfection. It is usually admitted that infection from the mother is more dangerous than that from other members of the family, and that the danger is the result of reinfection.

The clinical form of the disease is most important in prognosis. If when the diagnosis is made the tuberculosis is still localized in the glands, a less serious prognosis can be given. If the glandular barrier is broken down and there is mediastinal and hilus infiltration, the case must be regarded as very serious, although the author affirms that he has seen symptoms recede and apparent recovery result from tuberculin therapy. If signs of generalized tuberculosis are present and the Roentgen ray confirms the diagnosis of miliary tuberculosis or of acute caseous pneumonia, the case must be regarded as desperate. Chronic surgical tuberculosis is the only form which offers a good prognosis and is caused by a spontaneous autotuberculin therapy from the slow progressive penetration of tuberculin into the general circulation.

The behavior of the tuberculin reaction is the last factor to be considered in prognosis of tuberculosis of infants, and Combe thinks that valuable data regarding prognosis can be obtained from a series of Mantoux intradermal tests. The test is given every fifteen days with the same amount of tuberculin, and, if in these circumstances, the reaction each time becomes more marked, it must be inferred that there is an increasing amount of tuberculin secreted and that the lesion is becoming more aggravated. Combe calls this the Mantoux anaphylactic reaction. If, on the other hand, the intensity of the reaction diminishes in intensity each time, until it disappears, either the lesion is secreting less tuberculin or the organism is producing more antibodies which unite with the tuberculin. This reaction Combe calls Mantoux immunity and regards as of favorable import.

Combe considers still another question, namely, the duration of tuberculous disease in infants. He says that, so long as the disease is limited to the glands, it spreads slowly, may last months, and may even be cured. In case of spread through the blood vessels with a resulting miliary tuberculosis, the course is of only a few weeks' duration. In the case of a caseous pneumonia the duration is a few months. In tabes mesentericus and hilus tabes, death takes place from a progressive cachexia and the disease lasts two or even three years.

G. E. Permin[34] has studied the skin tuberculin test in regard to the prognosis of tuberculosis in infancy and concludes that only during the first year of life does a positive reaction indicate a grave outcome. His conclusions are based on tests performed on the children of patients who apply to the two antituberculosis dispensaries in Copenhagen. In all, forty-six tests were made. Of fifteen infants less than a year old, six died, but only two of thirty-one between 1 and 2 years. Many of the children who had been repeatedly exposed to infection seemed to thrive through quite a long period of observation.

PROPHYLAXIS

35. Knopf, S. A.: The Period of Life at which Infection from Tuberculosis Occurs most Frequently, Med. Rec., New York, 1916, **84,** 47.

36. Kingsley, S. C.: Program for the Promotion of the Physical Welfare of Children and the Prevention of Tuberculosis Among Them, Jour. Am. Med. Assn., 1916, **66,** 73.

37. Jeanneret, L.: Tuberculosis and the School, Rev. méd. de la Suisse romande, 1916, **36,** 449.

38. Weith: v. Pirquet Test in the Schools of Lucerne, Rev. méd. de la Suisse romande, 1916, **36,** 537.

39. Gwynn, W. C.: Protection of the Child from Tuberculous and Kindred Ills Through Adequate System of School Hygiene, Washington Med. Ann., 1916, **15,** 118.

40. Dana, H. W.: Tuberculous Infection in Children, Boston Med. and Surg. Jour., 1916, **174,** 755.

41. Jeanneret, L.: Prophylaxis of Tuberculous Meningitis and Miliary Tuberculosis in Children, Arch de méd. d. enfants, 1916, **19,** 414.

42. Ustvedt, Y.: Infant Mortality in Families Where There Is Tuberculosis, Norsk. Mag. f. Laegevidensk., 1916, **77,** 1301; Abstr. Jour. Am. Med. Assn., 1916, **67,** 1482.

43. Reckzch, P.: Predisposition to Tuberculosis, Arch. f. Kinderh., 1916, **65,** Nos. 3 and 4.

44. Stern, E.: Tuberculosis in Children, Ztschr. f. Tuberk., 1915, **24,** 436.

45. Schlesinger, O.: The Incidence of Tuberculosis Estimated by the v. Pirquet Cutaneous Test, Ztschr. f. Tuberk., 1916, **26,** 180.

46. Michie, H. C.: Tuberculosis Survey of an Alaska Eskimo Village, Med. Rec., New York, 1916, **90,** 663.

47. Rosenberg, J.: Value of Immunized Milk as a Prophylactic and Remedy for Tuberculosis, Med. Rec., New York, 1915, **88,** 917.

48. Pottenger, F. M.: The Nonspecific and the Specific Defense of the Child Against the Tubercle Bacilli, Jour. Am. Med. Assn., 1916, **67,** 1409.

S. A. Knopf[35] discusses the period of life at which infections from tuberculosis occur most frequently and how their frequency can be diminished and prevented from becoming tuberculous disease. He bases his conclusions not only on his own experience, but on the answers to forty letters to well-known specialists on tuberculosis and internists, and on twenty letters to well-known authorities on diseases of children. He adds to the results of this correspondence whatever important enlightenment he could find by perusal of the recent literature.

Summarizing the results of this study, Knopf says that the age at which a tuberculous infection contracted in infancy or childhood becomes active was, according to the majority of correspondents, at, or shortly after, 15 years; next, between 18 and 30 years. Nearly all of the authorities consulted unite in the opinion that, in order to combat tuberculosis successfully in the young and old, the sources of infection in childhood must be diminished, and Knopf enumerates the measures which he hopes may tend to diminish this frequency of infection, and, when it does occur, prevent the disease from developing. He says we must seek to amend the federal and state laws which make it a criminal offense for a duly licensed physician in good standing to give advice concerning the means of preventing conception. All cases of open tuberculosis should be required by law. to be reported to the health authorities, who in turn should be authorized to send the patient instructions to prevent infecting others. Cases which cannot be properly taken care of in the home, or when it is evident that they constitute centers of infection, should be transferred to sanatoriums, special hospitals, or at least to special wards in general hospitals.

For the pregnant tuberculous woman there should be a maternity sanatorium or a special ward in existing maternities, where prolonged antituberculous treatment can be effectually carried out, and where mothers can receive such instructions as will guard their offspring from postnatal infection. Where there is the slightest suspicion of tuberculous infection the child should have a healthy wetnurse or should be bottle fed. Enterprises for the purpose of providing medically supervised country homes for tuberculous mothers and their children should be helped by private philanthropy or by the aid of the municipality. All children under 5 years of age should be subjected annually, or even semiannually, to the von Pirquet test, and all who react positively and have symptoms and physical signs in addition should be placed under proper treatment. All children between 5 and 15 years of age, particularly those attending public schools, should be subjected to a careful physical examination on entering, and an annual reexamination thereafter, always accompanied by a von Pirquet test. Those reacting positively and showing physical signs, those evidently predisposed to tuberculosis, should be placed in open air classes, open air schools, preventoriums, seaside or inland sanatoriums. Open air instruction should be practiced, whenever feasible. Calisthenics, breathing exercises and swimming lessons should constitute a part of the curriculum of every public and private school. The school authorities should have the right to investigate the home of any child attending public school, when the teacher or school physician thinks that underfeeding, bad sanitary home environments, or child labor at home are responsible for a poor physical condition, which might develop into tuberculosis.

Child labor must be done away with. There should be an obligatory examination for tuberculosis and other serious diseases of every boy or girl prior to entering college or any occupation. There should be periodical examinations for tuberculosis of all employees. For those weeded out as tuberculous or afflicted with other diseases, there should be agricultural and industrial colonies. There also the graduates from sanatoriums should be sent for an opportunity to regain strength and vigor, to make their cure more lasting, and above all to learn again to earn their living. There should be state insurance or obligatory private insurance against accident, old age, and diseases, including tuberculosis, for all earning less than $1,000 per annum. Uniform bovine laws should be enforced by federal authorities in all states of the Union alike. With all this there must be continued propaganda for the education of the masses concerning the prevention of tuberculosis, alcoholism and other social diseases; for the improvement of housing conditions; for the prevention of injurious overwork; for healthful recreation of the masses in city and country; for the return to the soil from our overcrowded cities; and above all, for a living wage for all who labor honestly and efficiently, and a rational and speedy solution of the problem of unemployment.

The measures outlined will prevent a benign infection from becoming disease and render the young child or adolescent less likely to future infection by increasing the natural resistance. The most expedient way to carry out the suggested program would be by a federal commission on tuberculosis, as has been suggested by the writer a number of times.

S. C. Kingsley[36] outlines a program for the promotion of the physical welfare of children and the prevention of tuberculosis among them, which was drawn up by the committee appointed at the meeting of the Mississippi Valley Tuberculosis Conference.

The work was divided into two classes: 1. The creation and promotion of institutions and agencies for the care and relief of those who are the victims of the disease and for safeguarding their families and associates. 2. The conduct of a vigorous department of education and propaganda.

Under the first heading come: (a) careful medical examination of patients, and, through children's clinics, of children in families of tuberculous persons; (b) sufficient and efficient hospital provisions for advanced cases by municipalities and counties; (c) sanatoriums for incipient cases, with adequate provisions for children; (d) open air schools; (e) sanatorium extension work, equipment of porches, roofs, etc., and special home relief, including cooperation with city and county relief agencies and charities of the community; (f) medical examination of employees and inspection for promoting shop sanitation and wholesome working conditions; (g) Christmas seal campaign; (h) infant welfare movements.

The second division of work is the department of education and propaganda. Most effectual work can be done by arming and setting to work already organized forces in the community, of which the following are common: 1. the public school with its teachers and officers; 2. state and local boards of health; 3. board of county commissioners; 4. city or county medical societies; 5. the country editor; 6. granges and farmers' alliances; 7. labor unions and fraternal orders; 8. women's clubs; 9. church organizations.

All these agencies afford opportunities for the most vital cooperation. Definite study should be given to the plan of approach and to the preparation of material for the different groups.

L. Jeanneret[37] believes that the school should take the lead in the fight against tuberculosis. Three forms of tuberculosis are of especial interest to the school physician. In the first the bacilli are quiescent in the glands and do not reveal their presence by physical signs, except a positive reaction to tuberculin. The second form Jeanneret calls tuberculosis in evolution. From time to time the bacilli in the glands take on activity and produce signs of intoxication in the child. The physical development is retarded and the hypoplastic type of Hutinel is presented. In the third group are the active forms. Among 123 tuberculous children between 5 and 15 years of age the author found sixty tuberculinized, thirty-two with tuberculous glands, seven with active tuberculosis, eighteen with latent pulmonary tuberculosis, and six with other forms. Because of the small number of active cases there is little danger of the child acquiring the infection in the school.

Jeanneret considers the method by which the school authorities can most easily detect the disease. He says that every child should have a health chart on which should be recorded his weight once a month, and his height twice a year. The weight divided by the height gives a reliable index of the physiologic balance. The chart should record also the color of the skin and mucous membranes, any anomalies noticed, and the result of the von Pirquet test. The von Pirquet test is indispensable. Once positive, it need not be repeated, but if negative, it should be repeated every year. Jeanneret thinks a Roentgen-ray machine a valuable adjunct to the school's equipment. He calls attention also to the importance of excluding tuberculous teachers from the schools, insisting on a rigid examination for all candidates.

As soon as a child with tuberculosis is discovered in school, he should be placed in a proper institution. Beside the removal of active cases, Jeanneret mentions a number of other measures which protect the schoolchild. Hygiene of the schoolbuilding is important, pure air in the schoolroom, and proper methods of sweeping and cleaning. Lessons in personal hygiene also are important. Periods of stress should be guarded against. Between the years of 5 and 9 the school program should be simple, and periods of recreation frequent. Jeanneret regards sunshine as the surest preventive of tuberculosis, and advocates gymnastics and exercises in the open air with the upper part of the body exposed. For children between 6 and 12 years these exercises should be predominately thoracic.

Weith[38] does not agree with Jeanneret as to the value of the von Pirquet test in schoolchildren, or that it should be obligatory in all schools. In the first place he thinks that the test is not entirely devoid of danger, and quotes a number of reports of children with scrofulous affections suffering violent exacerbations of the skin affection after a von Pirquet test. He found also instances of phlyctenular conjunctivitis and of general disturbance after the test. Nor does he think the test infallible. He has found in the literature reports of cases in which necropsy showed no tuberculous lesion when there was a positive von Pirquet test during life, and, on the other hand, necropsy has sometimes shown tuberculous lesions, when the test was negative. He believes the von Pirquet is not absolutely necessary for the diagnosis of tuberculosis and quotes Jeanneret himself as saying that most children who give a positive reaction are frail, delicate, anemic and suffer from scrofula and general adenopathy. Weith believes that other means are much more important in diminishing tuberculosis among schoolchildren, improving hygiene in the home, propaganda against alcohol, etc.

W. C. Gwynn[39] emphasizes the fact that the protection of the child from infection with the tubercle bacillus can be obtained only by the exclusion from the public school of the open case of phthisis, in teacher and pupil. Any system of school inspection to be thorough must include the teacher, because of her close association with the pupils. Exclusion of pupil does not offer great difficulty, as tubercle bacilli are rarely found in the sputum of children and, when they are, the children are too sick to be benefited by attendance at school. Children with closed tuberculosis, which is the common type, should be segregated in open air schools, not only because this is the ideal method of treatment, but because it is never known when a closed case will become open and do incalculable harm before detection.

H. W. Dana,[40] from wide study among schoolchildren, concludes that the period for infection is frequently childhood, and that from this early infection follows most of the active tuberculosis of later life. He thinks the general practioner has not been interested in the diagnosis of tuberculous infection in children and has not awakened to its practical importance. In fact, the general practitioner tends to deny the existence of tuberculous infection in children.

According to Dana, it is a safe general rule to follow, that any child who shows constantly poor nutrition, fever, lack of vitality and ambition and abnormal pallor should have the benefit of fresh air, abundant and suitable food, as well as frequent, careful physical examination by an expert. Children suffering from tuberculous infection should be sought for by the school physician, and, when found, should be taken by the school or district nurse at stated intervals to the local tuberculosis dispensary for examination. Dana does not place much value on the Roentgen ray in distinguishing between cases needing active treatment and latent or healed cases.

L. Jeanneret[41] lays stress on the great importance of removing the new-born child from the home when there is a case of open tuberculosis. This is done as a prophylactic measure against tuberculous meningitis and miliary tuberculosis, forms of tuberculosis which are second only to gastro-intestinal diseases in mortality statistics of infancy. As soon as the child has passed its eighteenth or nineteenth month, when the greatest danger of generalization of the tuberculous infection is past, it can be restored to its parents, but even at this time advice in regard to prevention of infection must be given.

Jeanneret thinks the ideal way for taking care of infants of tuberculous parents is to organize institutions where the infant can be taken at birth and where the parents can visit the child and watch its progress without coming in direct contact with it.

In case the infant has already become infected, the author puts his faith in intradermal injections of tuberculin as a prophylactic measure against generalization of the infection. This method creates in the skin a focus from which tuberculin is gradually absorbed into the general circulation and stimulates the production of specific antibodies. The artificial focus is maintained by repeated injections.

Intradermal injections are simple and easy. The skin is pinched up into a fold and the very fine needle is introduced, parallel to the surface. Jeanneret injects 0.01 c.c. of a 1 : 1,000 solution, repeating the injection every third day and increasing the strength very gradually, till 0.1 c.c. of a 1 : 10 solution is reached. The local reaction is less in infants than in older children. As the child grows older it manufactures its own tuberculin in its tuberculous glands and does not need artificial tuberculinization. Jeanneret is confident that he has saved certain infants by these prompt measures and does not hesitate to recommend them even when the prognosis is grave.

Y. Ustvedt[42] has compiled infant mortality statistics in tuberculous families. He thinks that unquestionably valuable lessons can be deduced from such figures. His material includes 480 infants born in families with one or more members suffering from tuberculosis in the contagious stage. An average of 19.2 per cent. of these infants died during the first year of life, while the average infant mortality in the city at large was 10.8 per cent. Ustvedt comments that these figures teach nothing new, but they emphasize the vital importance of removing infants at once from a tuberculous environment, and especially from a tuberculous mother.

P. Reckzch[43] says that so important is an early diagnosis of tuberculosis that we must begin in infancy to seek for symptoms and signs of the disease, and continue to seek for them throughout childhood and puberty, if we would prevent the later ravages. Predisposing factors to tuberculosis are found in underfeeding, overwork, and infectious diseases. These factors may act in the parents and through them in the new-born child, even when the parents give no evidence of tuberculosis. The larger the number of relatives in a family who have had tuberculosis, the greater the predisposition of the child. Descendants of tuberculous parents succumb to phthisis more often than descendants of normal parents. They are easy prey to other infections also. In large families it is found that the younger members to whom less of the mother's vitality is given are the commoner victims of tuberculosis. Where there is this predisposition, the children suffer from other infections, as diphtheria, scarlet fever. If both parents have died of tuberculosis, the predisposition of the child is greater than if only one had died of the disease. The nearer the birth of the child comes to the death of the parent, the greater the predisposition and the greater likelihood of death. Children having latent tuberculous infection in the lymphatic system are subject to other infections, especially in the organs of the respiratory system, and convalescence is slower than in the normal child.

From a study of statistics in Alsace and Lorraine between the years 1905 and 1912, E. Stern[44] has obtained some instructive figures regarding the mortality of tuberculosis in children. The general decrease during this period was 7.5 per cent. In the first year of life this decrease was greatest, due doubtless to the results of infant welfare propaganda; perhaps also to the lowered birth rate which it has been shown existed during this period. In the following period, from 1 to 2 years, the decrease was less marked, 9.6 per cent. In the third year the decrease was 4.8 per cent., and in the period from 3 to 5 years, 8.9 per cent. During the first half of the school years, namely, from 5 to 10 years, the decrease in deaths from tuberculosis was only 4.4 per cent., and Stern thinks this is due for the most part to the influence of school life. The child has new and unaccustomed surroundings, associates with many other children and is compelled to work several hours a day in a closed room. The slightest decrease occurred, however, between the ages of 10 and 15 years, when it was only 2.2 per cent. Puberty here played a very important rôle.

Stern thinks that social workers should take heed of the fact that statistics show a slighter decrease in the mortality from tuberculosis at school age and should institute means of improving home and school hygiene and of giving instruction in personal hygiene, movements which will doubtless result in lowering the mortality statistics for this period. The physician also should do his share in the work.

O. Schlesinger[45] emphasizes the value and harmlessness of the von Pirquet test and the ease with which the reaction is interpreted. He reviews and summarizes reports of the results of this test on hundreds of children and adults in various countries. Analysis of these reports shows that in remote regions having little intercourse with cities, where tuberculosis is always prevalent, the disease has very little foothold. The more the region is visited by people from the cities, the more widespread it becomes. In villages and towns tuberculosis spreads very gradually, probably through the school. In medium-sized cities the children become infected before the school age, while in the large cities a considerable number become infected during the first years of life. Schlesinger comments on the well known fact that tuberculosis takes a much more severe form and a more rapid course among uncivilized than among civilized people, and he believes this is because the latter acquire an immunity through reinfection. He thinks, too, that this acquired immunity explains the lowered mortality from tuberculosis in the last few years in England and Germany.

H. C. Michie,[46] making the von Pirquet test on nearly all children in the Eskimo village on St. Michael's Island, found that 61.5 per cent.

were tuberculous. After a survey of their homes and of the sanitary conditions of the village, he concludes that the environment of these children is such that tuberculosis must increase among them, and that there is a great field for medical missionary work.

J. Rosenberg[47] asks of the medical profession cooperation in furthering the use of immunized milk as a prophylactic measure and remedy for tuberculosis, and impresses the urgent need of facilities and means to produce and supply immunized milk. The author believes in the ultimate control of the great white plague, but not by methods now emphasized, for their inadequacy is proved by the present death rate. The principal cause of failure lies in the fact that the main entrance gate for infection is unguarded. While attacking every possibility of communicating the disease from man to man, the diseased cow is left undisturbed. Cattle tuberculosis is rapidly increasing and is undoubtedly the cause of extensive infection and illness among young children. Rosenberg believes that tuberculosis in cattle can be eradicated by prophylactic injections of bacillary emulsion prepared from dead cultures of both the bovine and human type of tubercle bacilli. This protective vaccination safeguards the healthy cow against infection by her stable companion, and also produces a supply of immunized milk, a remedy for patients infected with tuberculosis. Immunized milk possesses antibacterial qualities like the blood of animals which have been immunized. It is a dilute antitoxic and bactericidal serum. Drinking the milk transmits the antibodies which pass through the intestinal mucous membrane into the general circulation and offer the same immunity as inoculation with antitoxins and antibactericidal serum. The writer reports a number of cases of pulmonary tuberculosis and of tuberculosis of the bones and joints successfully treated with immunized milk. He quotes also the report of Castelli of the University of Genoa, who indorses the claim that protective vaccination secures the cows complete immunity against bovine tuberculosis; that feeding infants immunized milk eliminates the principal source of tuberculosis, and that it is a remedy for every type of tuberculosis.

F. M. Pottenger[48] calls attention to the protective rôle of the lymphatic system against invading bacteria, specially tubercle bacilli. He says that collections of lymphatic tissue, as tonsils, adenoids and Peyer's patches are placed where bacteria are likely to gain entrance to the tissues so that they may be taken up by them and destroyed. He particularly emphasizes the importance of this protective mechanism because of the tendency of ruthlessly sacrificing lymphatic structures in the throat and vault of the pharynx without giving due consideration to their importance. He says he is aware of the fact that tonsils and adenoids must be removed, but he believes that unless they are producing distinctly harmful effects they should be left in situ until the child is old enough to have come in contact with pathogenic bacteria in sufficient numbers to have developed a specific cellular defense against them.

TREATMENT

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The following review of L. Jeanneret's[49] book on "Treatment of Medical and Surgical Forms of Tuberculosis" is of especial interest, as heretofore very little mention has been made of the method of treating tuberculosis by intradermal injections of tuberculin.

Following out the idea of Mantoux, Jeanneret uses the intradermal injections of tuberculin as a measure of the patients' specific sensibility and as a therapeutic agent. Subcutaneous injections of tuberculin in infants are useless in determining sensitiveness, because, if the dose is pushed so as to produce a reaction, namely, fever, rapid pulse, loss of weight, and congestion of the tuberculous focus, there is great danger of producing a generalization of the disease. Intradermal injections, on the other hand, cause only a local reaction and are perfectly harmless. Jeanneret observed a febrile reaction in only twenty of 4,000 cases, or 1 per cent., in 200. Moreover, this method is a very simple means of measuring the specific sensitiveness of the patient. All that is necessary is to measure the diameter of the reaction at its height, that is, at the end of forty-eight hours. Jeanneret usually injects as a test, $\frac{1}{10}$ mg., a dose ten times stronger than that recommended by Mantoux. Intradermal injections do not cause any reaction in the nontuberculous, but in infected persons, whether the process is latent, active or cured, it gives rise to a local reaction, except when the affected individual is cachectic or suffering from acute infectious diseases.

Jeanneret has found that the sensitiveness to intradermal injections varies with the forms and localization of the tuberculous process. Children without manifest symptoms show little sensitiveness to the injections. The reaction averaged 6 mm. in diameter in 800 such instances. Children with a healed clinical tuberculosis always remain sensitive and the intradermal reaction oscillates around 10 mm. Children with tuberculosis of the tracheobronchial glands are more sensitive and give a reaction 14 mm. in diameter. Children with pulmonary lesions show a hypersensitiveness and an intradermal reaction of around 30 mm. in diameter. In this form the reactions are very irregular. Exacerbations of the disease cause an increase, and amelioration a diminution, in diameter of the reaction. Marked irregularity as well as increase in dimensions of the reaction are of unfavorable prognostic significance. Children with osseous tuberculosis give an intense intradermal reaction of 20 to 30 mm. in diameter. In favorable cases it remains stationary or gradually diminishes until a cure is established. In unfavorable cases it increases in size until just before death, when it disappears. Children with tuberculous pleurisy usually show a marked reaction, 35 to 40 mm., those with tuberculous peritonitis a feeble reaction. Strongest reactions are observed in children with tuberculous polyserositis. In these cases the reaction is often 50 to 60 mm. in diameter. Sensitiveness is also marked in cases of renal tuberculosis. It disappears gradually after extirpation of the diseased kidney. In meningitis and miliary tuberculosis the reaction measures from 15 to 35 mm. and disappears completely just before death.

Jeanneret thinks intradermal injections valuable in the treatment of tuberculosis. He believes that by this method foci are established in the skin from which the tuberculin is gradually absorbed and by which immunity is established. He compares this immunity to that established by absorption of tuberculin from tuberculous glands. Jeanneret uses Koch's old tuberculin for the injections and makes up six solutions diluted so that 1/10 c.c. of each contains 1 mg.; 1/10 mg., 1/100, 1/1,000, 1/10,000 and 1/100,000 mg. of tuberculin. The initial dose for hypersensitive patients is 1/100 mg.; for those less sensitive, 1/10 mg. If the resulting reaction is more than 10 to 15 mm. in diameter, the dose is reduced. If it is less than 3 to 4 mm., the dose is increased. As a rule, an effort is made to maintain a reaction of 5 to 8 mm. The same dose is repeated if the reaction remains this size, the interval between doses being from five to ten days. If the sensitiveness becomes more marked, the interval is increased and diminished again, as the sensitiveness diminishes. The duration of the treatment depends on the clinical condition of the patient; Jeanneret advises it continued even after a cure is established. In unfavorable cases when, in spite of smaller doses, the reaction remains marked without any tendency to diminish, the treatment must be given up.

Jeanneret is very enthusiastic over the results he has obtained with this method of treatment, and he believes tuberculin given in this way has a curative action even in grave and progressive forms of tuberculosis.

W. W. Howell[50] says treatment of tuberculosis in infancy is essentially the treatment of the primary lesion and preventing the disease from spreading beyond it. The important factors in the treatment are food, fresh air and rest; and these measures must be persisted in long enough to insure good nutrition and a gain in weight. As long as the tuberculosis is kept primary, the infant is safe, but, unless the disease is recognized before the secondary forms develop, little or nothing can be done in the way of treatment.

H. J. Gauvain[51] says it may be stated emphatically that some of the extravagant claims made as to the value of sun treatment of tuberculosis cannot be substantiated. Sunlight alone is not sufficient for the cure of the majority of the severe types; rather it should be regarded as an important adjuvant treatment, to be employed with care and discrimination. In certain cases its application is without benefit, and is attended by actual danger.

Gauvain summarizes the action of sunlight as follows: On the local lesions it has at first a direct effect. Superficial micro-organisms are destroyed or inhibited by the sterilizing action of the light waves, and this action is assisted by the inflammatory response which results from a reasonable exposure to strong sunlight. Since tuberculosis must be regarded as a general constitutional disease, the more remote effects of sunlight may be reasonably anticipated to be more important in producing its arrest. Remote beneficial effects cannot be obtained without pigmentation of the skin. Pigmentation is not sufficient to produce improvement, but it is a medium through which improvement is obtained. The most marked outward benefit of successful insolation is the extraordinary tonic effects which usually accrue.

The author has formulated a number of rules which must be observed when this treatment is given: 1. The patient's head must always be protected. 2. The patient must never be allowed to become too cold or too hot. 3. On the first day the legs to the knees may be exposed hourly for five minutes. If this is tolerated well, exposure of the knees may last for ten minutes hourly. On the third day exposure of the thighs for ten minutes hourly, and on the fourth day, similar exposure for fifteen minutes may be attempted. On the fifth day exposure of the thighs for fifteen minutes and of the body for five minutes is desirable. On the sixth day exposure of the thighs for fifteen minutes and of the body for ten minutes hourly may be attempted. If the patient is pigmented, the periods of exposure may be gradually increased, until the patient may be completely exposed for periods, and, when pigmentation is fully established, continuous exposure may be undertaken. 4. Blistering must be carefully avoided. 5. If the temperature exceeds 100 F., the patient should not be exposed the following day, unless special orders are given. 6. Sinuses should be exposed and any purulent discharge from them should be immediately swabbed. 7. A nurse must be on duty during the whole time.

C. N. Dowd[53] draws rather definite conclusions regarding the treatment of tuberculosis of the cervical lymph nodes based on the study of 687 cases, in which the operation was performed by himself or by his associates, and which were kept under observation for twenty-two years. He places his patients in three groups, according to the stage of tuberculous process. In group one are the patients in the early stage of the disease. Tubercle bacilli, he says, are inhaled with the air or swallowed with the food and lodge in the crypts of the tonsils, faucial and pharyngeal. The route of infection from the tonsil to the tonsillar lymph node is a very short one, and the invading tubercle bacilli cause swelling, fibrosis, caseation and possibly abscess formation. If the defense of the gland holds, the process remains local and extends very little beyond the upper group of lymph nodes. Of the 687 patients who form the basis of this paper, 432 were observed in this stage. Ninety-one per cent. of the patients were apparently cured, when last seen, and the writer thinks the results eminently successful.

In group two Dowd places patients with glandular abscesses or sinuses or with enlarged glands extending along the entire jugular chain and along the border of the trapezius muscle. There were 385 patients in this group, and 68.2 per cent. made apparent recoveries. The results obtained in this group were greatly inferior to those in the first, and the writer thinks it would have been much better for these patients to have undergone an operation, while the disease was in its early stage.

In group three are patients showing little power of resistance to tuberculosis. There is involvement of a great number of nodes and usually evidence of tuberculosis in other parts of the body. In this group were fifty patients, and only 35 per cent. were apparently cured. Treatment of this type of cases is far from satisfactory.

Commenting on the subject of tuberculosis of the cervical lymph glands, Dowd says much confusion exists about the term "operation" as applied to these cases. He says that if the incision of an abscess or the removal of a single gland is called an operation, the operative results will be very poor; if the term operation means the removal of all enlarged lymph nodes of the neck, the results will be very good.

In discussing Dowd's paper, J. F. Golden[54] says that tuberculosis of the cervical lymph glands in children has a tendency to cure itself without the aid of surgical intervention. He has found the tuberculin method the best, together with the administration of fats in the forms of emulsion of cod-liver oil, butter and cream. He has secured by this method a recession of glands, some of them breaking down and discharging a cheesy substance, but uniformly progressing to a cure without enucleation.

R. T. Morris[54] thinks that the majority of cases of tuberculosis of the lymph glands of the neck do not require operation at all, provided that the patient is so situated at hospital or in the private house that he may have full benefit of professional knowledge on the subject. He emphasizes the importance of using tuberculin properly, but believes the best way of dealing with these cases is along the lines of the Bier idea of hyperemia. He has the patient rest the neck against a hot-water bag for several minutes, then an ice-bag, again the hot-water bag for several minutes, then the ice-bag. Morris has also obtained some good results with the Roentgen ray.

W. E. Ladd[54] has for the last four or five years been following the teaching of Dr. Dowd. He has operated in about 160 cases of cervical adenitis, mostly in children. One hundred and thirty of these have been followed for from six months to five years. Of these, 93 per cent. are apparently cured. Ladd emphasizes the importance of removing the tonsil at the same time as the cervical glands. In his series of cases the tonsil was believed to harbor the primary focus in 75 or 80 per cent. of the cases. Ladd believes that if one waits to try tuberculin, hygiene without operation, Roentgen ray and other forms of treatment, a great many cases will progress to tuberculosis which is more disseminated and more difficult to cure.

A. F. Holding[55] has observed the good effects of Roentgen ray on tuberculous glands and is surprised that the method is so little known and seldom advised by the medical profession. The efficacy of the Roentgen-ray treatment on this condition has been demonstrated in surgical clinics and the literature contains reports of 1,500 cases successfully treated. Surgical treatment was orthodox before the discovery of the Roentgen ray, and its therapeutic value is still advised by a large number of physicians. Holding thinks that nonsurgical methods, including Roentgen ray, deep hyperemia and tuberculin should be tried before any patient is submitted to radical operation.

E. Albert-Weil[56] divides tuberculous adenitis into two groups, the inflammatory and the suppurative. The latter he subdivides into closed forms and forms associated with fistulae and cutaneous tuberculosis. He thinks all forms amenable to treatment with the Roentgen ray. In the inflammatory forms the Roentgen ray leads to the disappearance of large masses of glands, but heliotherapy and medical treatment are necessary to combat the tuberculous diathesis and increase the resistance of the patient. In closed suppurative adenitis it is well to evacuate the pus by puncture with a fine needle, as the pus prevents the penetration of the Roentgen ray. In the form with fistula, Weil clears out the fistula and suppurating focus and then applies the Roentgen ray. Weil gives several illustrations of how the enlarged glands recede, even when they are of months' duration.

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AMYOTONIA CONGENITA: A SURVEY OF THE KNOWN CASES WITH A REPORT OF THREE NEW CASES *

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Since Oppenheim[1] in 1900 first described this disease, case reports have gradually accumulated until at the time of writing 115 are on record, with 27 anatomic reports, including necropsies and muscle biopsies. A mass of clinical and pathologic material of these proportions appears to be great enough to render a statistical analysis of considerable value, not only in defining the disease more precisely, but in throwing new light on the etiology and in correcting some current misconceptions.

Reviews of the literature have been frequently made by those reporting new cases. It will suffice to mention the more important of these, noting that the last fairly comprehensive study — Thorspecken's — appeared more than four years ago, and that none is based on the statistical method. Batten, in 1903, without mentioning Oppenheim's description, reported three cases under the name of "myopathy — infantile type." Kundt in 1905 described a case and reviewed the subject. Collier and Wilson in 1908 collected the twenty-six then known cases, including four new ones, and gave us the masterly description which is the classic of this subject. Rothmann in 1909, Chéné in 1910, Habermann in the same year, Griffith in 1910 and 1911, Cassirer in 1911 and Thorspecken in 1912 all made careful studies of the disease. Concetti also surveyed the literature, but his paper, besides being incomplete in many points, has the disadvantage of not being generally available to the medical public. The painstaking necropsies of Marburg, Kaumheimer, Rothmann, and Foot have added greatly to our knowledge of the histologic changes in the muscles and nervous system, and their communications contain careful reviews of special phases of the subject. Of the 115 cases reported, 29 were from

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[1] References will be found arranged alphabetically at the end of the article.

Germany and Austria, 21 from the British Isles, 15 from France, 25 from Italy, 1 from Holland, and 24 from America.

The following synopsis is based on a tabulation of the 115 cases reported in the literature which appear to be properly diagnosed.

DEFINITION

A disease beginning at birth or in early infancy due to a congenital developmental defect of the lower motor neuron and of the voluntary muscles, clinically characterized by weakness, hypotonia and a quantitatively diminished electrical response in the muscles, usually without disturbances of a sensation or of mentality.

ETIOLOGY

Syphilis and other infections play no part. A positive Wassermann reaction was reported but once (Gordon's incompletely reported case), and in the nine other cases this test was negative. The von Pirquet tuberculin test was three times negative; never positive.

Since the pathology of amyotonia congenita furnishes strong evidence for the hypothesis of a congenital defect, it is a matter of particular importance to scrutinize the case reports carefully for clinical evidence of *hereditary* or *reproductive defects.* All the earlier writers dismiss such evidence as accidental, or state simply that heredity plays no part. The statistical study does not justify such an inference. Thus, the fact that *quickening* was absent (6), weak (12) or retarded (2) in 54 per cent.[2] of the thirty-seven cases in which notes were made of this point and normal in only 5.4 per cent. (present, degree not noted in 40.5 per cent.) proves clinically that the disease is certainly present before birth. That the pregnancies, with but two exceptions, ran a normal course to birth at full term, indicates that incidents of gestation have little to do in producing it. Familial occurrence is found three times, and these cases are by no means atypical, the two cases reported by Sorgente having been excluded by Collier and Wilson only by reason of familial occurrence, which is obviously begging the question. Skoog's familial cases were brothers, while those of Sorgente and of Concetti were brother and sister: all were successive births. Furthermore, Silvestri records the fact that a brother of his patient was paralytic at birth, and Reiner, that his patient was one of twins, the other of which died intrapartum. The second case reported by Collier and Wilson themselves was the first of three children. The second child was said to have had "something wrong with the limbs" and the third died a few days after birth. The mother had been weak as a child and several members of her family presented the peculiar symptom of having difficulty in closing the eyes. A study of the patients' places in the order of birth is decidedly suggestive of the possibility of *reproductive exhaustion* as a factor in the production of the disease. Unfortunately I find notes on this point in only sixteen instances. Of these, eight, or 53 per cent., were born of the fourth or a later pregnancy.

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[2] All percentages are based on the number of cases in which we have data bearing on the particular point under discussion.

1st child	2*	6th child	1
2nd child	3*	7th child	1
3d child	2	8th child	1
4th child	1	9th child	1
5th child	3	10th child	1

* Including Concetti's familial cases.

It is unfortunate that the ages of the parents have been so rarely recorded. In one of our cases the mother was 40 years of age and approaching the menopause. In one of Concetti's cases the father was 58 and the mother 50. In our third case the mother was 28; she had had an abortion about nine months before the birth of our patient. These facts strongly suggest an analogy between mongolism and amyotonia congenita. One of Concetti's cases seems to supply the link, having typical symptoms of amyotonia congenita and a mongolian facies. This analogy, or rather, relationship, is the more strongly suggested when some of the symptoms of mongolism are remembered, such as the tonelessness of the muscles and the hypermobility of the joints. This point will be more fully discussed in another communication, but it may be said that we have already found the typical myatonic electrical reaction in three cases of mongolism.

PATHOLOGY

Muscles.—Macroscopically, the muscles are nearly always described as pale, soft, or flabby. Foot compares the appearance to that of raw pork. Sometimes very little muscle tissue is visible. The fatty infiltration appears to be constant in the affected muscles. The degree of muscular involvement varies greatly in different muscle groups. The diaphragm has always been found normal, except in Foot's case, in which some slight abnormalities in staining properties were discovered in this muscle. The muscle fibers themselves are characteristically of diminutive size. The small fibers vary in size from those consisting of only one or a few fibrillae, as in Marburg's report, to those of nearly normal diameter (Mensi). Fibers of normal size were found to be present in most of the later necropsies (Archangelsy and Abrikosoff, Councilman and Dunn, Marburg, Strauch) and probably always occur in the less severely affected muscles. There can be little question that hypertrophied fibers do occur in some cases. The measurements made by Collier and Holmes (diameter of fibers 100 to 150 microns) leave little doubt on this point. Hypertrophic fibers were also noted by Baudouin, Lereboullet and Baudouin, Griffith and Spiller, Archangelsky and Abrikosoff, Kaumheimer and Concetti, but exact measurements were not made. Councilman and Dunn in 1911 determined in their case that the larger fibers were actually of normal size, but appeared large by contrast with the diminutive fibers, an observation repeated and confirmed by Marburg, Foot, Skoog, and Strauch, all of whom failed to find fibers larger than the normal.

The cross striations are usually well preserved. Reyher and Helmholz found them indistinct or absent, Councilman and Dunn, absent in a few; Skoog notes that they were lost in the majority of the fibers; Strauch found them less distinct than normal, and Openshaw states that they were absent. For a full description of the finer histologic changes the paper of Foot should be consulted. Nearly all the early examinations showed an increase of the sarcolemma nuclei, which in some cases (Collier and Holmes) was described as enormous. Archangelsky was the first to note that this increase is not an increase over the normal number, but only relative to the size of the muscle fibers, an observation which has been confirmed by most of the later necropsies. Apparently regressive change in the muscle affects only the sarcoplasm which becomes reduced in volume, while the sarcolemma nuclei remain unchanged in numbers. With the exception of Archangelsky and Abrikosoff and Concetti, all observers found a striking increase in the fat and connective tissue in the muscles. This points strongly to a process of replacement, though Foot disputes this on grounds which seem to me inconclusive. True degenerative changes in the muscles are exceptional, and, in my opinion, not a part of the disease.

In the majority of cases in which a careful examination has been made, the peripheral nerves have shown deficient myelinization of the fibers, with an increase of the connective tissue of the perineurium and endoneurium. In Spiller's case the nerves are stated to have been normal. Kaumheimer found an actual decrease in the number of fibers, but no axis cylinder without its medullary sheath, and Rothmann noted that the fibers themselves were small, with distinct medullary sheaths. It seems fair to conclude that the essential defect in these nerve fibers is either an insufficient supply or a complete lack of myelin in the medullary sheath, both in the peripheral motor nerves and in the motor tracts of the cord. The defective myelinization varies greatly in extent and localization in different cases, though usually selecting the lower motor neuron, and apparently is never universal, at least in viable infants.

Degeneration has been found only exceptionally. Griffith and Spiller found the posterior tibial nerve much degenerated. Councilman and Dunn found a few degenerated fibers. Some doubt is thrown on the truth of these deductions by the fact that unless performed on perfectly fresh tissue, the Marchi stain is apt to give some discoloration of what was a normal nerve, because of postmortem changes in the myelin. Degeneration, it seems safe to conclude, is not an essential part of the amyotonic process. Changes similar to those described in the peripheral nerves are encountered to a greater degree in the anterior roots, which according to all observers excepting Spiller and Lereboullet and Baudouin, are reduced in size and contain many fibers deficient in myelin. The posterior roots, on the contrary, are practically never involved (in Rothmann's case they were somewhat atrophic at the cervical level only). Spiller and Lereboullet and Baudouin found no changes in the anterior horns, and Councilmann and Dunn note only that the cells did not appear to be reduced in number, but all the other necropsies showed striking changes here. Reduction in the number of cells was always present, and absence of the large ganglion cells is noted by Mensi, Concetti and Rothmann. The cells which did occur were sometimes misshapen, sometimes pyknotic and in one case vacuolated (Foot). Changes in the posterior horns, on the other hand, were very rarely found. Rothmann states that in his case the cells were fewer than normal. Clarke's column also appears to be spared as a rule, but Marburg, Kaumheimer and Rothmann found some changes — reduction of number or absence of large cells. The cord tracts showed only deficient myelinization, except in Kaumheimer's case, in which a few degenerated fibers were seen. The brain, cerebellum and medulla are only exceptionally involved. Reduction in the number of cells, in one case with chromatolysis, was twice found (Kaumheimer and Rothmann) in the hypoglossus nucleus; in neither case was involvement of the tongue noted clinically. Berghinz found microgyria and hypoplasia of the cerebrum and cerebellum, with a decrease in the number of the cells. Concetti found that all the layers of the cerebral cortex were reduced in volume, with fewer than the normal number of cells.

An increase of neuroglia in the cord, and in one case in a few places in the cerebrum (Kaumheimer)— apparently a replacement process analogous to that in the muscles — is noted by Marburg, Foot, Kaumheimer and Rothmann, the last named also noting an increase in the vessels. Concetti made the isolated observation that the Purkinje cells of the cerebellum were reduced in number and altered in shape.

Vascular changes have been present in several cases. Thickening of the walls, due to an increase in the adventitia, are noted by Collier and Holmes, Griffith and Spiller, Rothmann, and Skoog. Intimal changes are usually absent, but Collier and Holmes noted some proliferation. Collier and Holmes also made the interesting observation that foci of small cells occurred at intervals around the vessels, and it is interesting that Foot also found areas of small cell infiltration in the rectus abdominis. These two observations, however, do not appear to be sufficient evidence for accepting inflammation as a factor in the disease, and the inflammation may perhaps be regarded rather as a complication. The heart, except in one instance, was normal. Griffith and Spiller found that the protoplasm of the cardiac muscle was rather granular and that there was an excess of polar pigment.

The thymus, thyroid and adrenals have been examined in a majority of the necropsies and, with but few exceptions, have been found normal. Griffith and Spiller note an absence of the chromaffinic cells in the adrenals and one observer (the reference has unfortunately been lost) found a hemorrhage in the adrenal. Baudouin found sclerosis of the thymus and thyroid.

Rigor mortis, when noted (six cases), was absent.

A point which has been too little emphasized in earlier summaries and which I think deserves emphasis is the pathologic change in the muscular nerve-endings. Of those who make notes on this point, only Archangelsky and Abrikosoff say that the nerve-endings were normal. Councilman and Dunn could find no nerve-endings in the affected muscles. Foot states that normal nerve-endings were found in the normal fibers, but that none were found in the small fibers. Rothmann observed that while the nerve fibers could be seen entering the affected muscle fibers, the end-plates were absent. Mensi was unable to find nerve-endings in his five necropsies.

A review of the necropsy findings in amyotonia congenita gives one the definite conception of a failure of the peripheral motor neuron in its entirety to develop, and strengthens the analogy to Little's disease, to which Collier has drawn attention. With the exception of two early necropsies, these changes, differing in extent and severity to be sure, have invariably been found. The writer states his opinion for what it may be worth, that the primary lesion of amyotonia congenita is a congenital hypoplasia of the lower motor neuron, believing that the muscular changes are secondary to this process, and that it will be found that the original fault is in the defective germ plasm of reproductively exhausted parents.

SYMPTOMS

The *time of onset* was not noted or not known in 10 cases. Of the remaining 105, symptoms of weakness or "paralysis" were noticed at or soon after birth in 86, or 81.9 per cent. In 2 cases they were observed during the first month, without antecedent illness; during the second month, in 2; at 3 months in 3; at 5 months in 1; at 6 months in 4; at 11 months in 1; at 12 months in 1, and at 14 months in 1. It seems likely that the failure to note symptoms at birth may be due to faulty powers of observation on the part of the parents (as Collier and Wilson point out), or that during the first three months of life hypotonia may be masked by the physiologic weakness of early infancy. In addition to the above-mentioned cases, it was asserted in four instances by the parents that the patient was normal until after illness or some other disturbance. In one case the disease was said to have followed a diarrhea at 1 month; in another, bronchopneumonia at 7 weeks; in a third, weaning at 3 months was the ascribed cause; and in a fourth, symptoms appear to have been absent until 18 months, developing after an attack of measles.

The *sexes* are represented in the proportion of 55 males (53 per cent.) to 48 females (47 per cent.).

Distribution of Muscular Weakness.—The lower extremities are the only parts found to be always involved. The frequency of involvement of the different parts of the body is shown by the accompanying table.

TABLE SHOWING FREQUENCY OF INVOLVEMENT OF DIFFERENT PARTS OF THE BODY

	No. Cases With Involvement	No. Cases Without Involvement.	No Records.	Percentage Involved of Cases with Record.
Lower extremities	107	0	8	100
Upper extremities	79	6	30	93
Thoracic respiratory muscles *	26	3	86	90
Trunk †	73	7	35	91
Neck	65	11	39	86
Face ‡	20	48	47	29
Muscles of deglutition	5	—	—	—
Abdomen §	22	—	—	—

* As shown by weak or absent thoracic respiration.

† As shown by inability to sit upright or to hold spine erect.

‡ As shown by lack of expression, or "apathetic," "inert," or "indifferent" expression.

§ "Protuberant," "weak," "soft," "atonic," "distended," "tympanitic," etc.

The inability to sit upright, so characteristic of this disease, is due partly to weakness of the muscles of the pelvic girdle, and partly to weakness of the muscles which support the spine.

Two points brought out by the statistical survey are contrary to the generally accepted view, namely, the not unusual involvement of the muscles of the face and others supplied by the cranial nerves, and of the intercostals. That the muscles of mastication and deglutition are usually spared is undeniable, and, on the whole, the facial muscles show less evidence of weakness than those of the trunk and extremities. It must, however, be remembered that none of the so-called muscles of expression are called on for work proportionally as great as that thrown on those of the extremities and trunk which also have to act against gravity, and that, since it is rare for any of the muscles to be completely unable to perform voluntary movements, it is possible that the same degree of involvement would find less expression in the facial muscles than in others. Involvement of the muscles of deglutition, which are supposed to be invariably spared, was specifically mentioned as present in 5 cases. Other instances of involvement of muscles innervated by the cranial nerves are supplied by the occurrence of nystagmus in 3 cases, of strabismus in 4, and of ptosis in 1. As regards involvement of the intercostals, the statistics practically refute the statement of Collier and Holmes (see reference to Brain, 1909, **32**, 274) that the "intercostals" act "well, as seems to be the invariable rule in this disease." In my own case the absence of thoracic breathing was evident and striking; in one other case the intercostals were specifically mentioned as being involved, in 13 others thoracic respiration was absent, and in 11 diminished; in only 3 was respiration said to be normal or negative. The diaphragm is practically never involved, though Foot describes changes in the staining properties of this muscle. It is clear that nearly any muscle may be involved in this disease, though individual cases vary greatly from one another in the distribution of weakness.

The *sphincters* have never been found abnormal, though sphincter involvement is difficult to determine in early infancy. Although *atrophy* in the sense of diminished muscular volume resulting from a retrograde process is usually stated to be absent in amyotonia congenita, the muscles are small, infiltrated with fat and the individual fibers are much less than normal in size. Atrophy as such was noted in two cases, one of which is classed by Griffith as doubtful.

Tendon Reflexes.—I have taken the knee-jerks as representative of these, though in some instances they are grouped with other reactions and reported simply as tendon reflexes. They were tested in 94 cases and were absent in 69, or 73.4 per cent.; diminished in 17, or 18.1 per cent.; present, degree not noted, in 5, or 5.3 per cent., and normal in 2, or 2.1 per cent. In one case they returned after an absence of five years. They were therefore present in 26.6 per cent. of the cases, and it is unjustifiable, contrary to the usual belief, to exclude the diagnosis of amyotonia congenita because of the presence of the patellar reflex. The other tendon reflexes such as the biceps, triceps and achilles jerks are also frequently absent.

The *superficial reflexes* are so variously reported that for statistical purposes they are best grouped, with the understanding that probably in most cases only the abdominal were tested. They were present in

20, or 50 per cent., of those in which records are at hand; absent in 20, or 50 per cent. In 2 cases the upper abdominal reflexes were present and the lower absent. In 1 they were described as "sluggish."

The Babinski, Oppenheim and Gordon reflexes were found present a few times, but nearly always before the walking age and were therefore of little significance. *Sensation* was normal in forty-four, or 91.7 per cent. of cases of which we have data. In one the pain sense, and in one "sensation" was doubtfully diminished. In only one instance was there a fairly definite history of diminution of sensation, and at a later examination it was found normal. To the almost invariable rule of normal sensation there is one exception, frequently commented on by observers, namely, the remarkable lessening of sensitiveness to the discomfort caused by strong faradic currents, a point which appears to be of considerable diagnostic significance.

Electrical Reactions.—The "myatonic reaction" of Collier and Wilson consists in a quantitative diminution of electrical irritability without the qualitative changes of degeneration. It is of all degrees of intensity, varying from a slight diminution of faradic irritability to absence of reaction to both forms of current. In the eighty-two cases of which we have notes, 82.9 per cent. showed the myatonic reaction, 6.1 per cent. were said to be normal, and 4.9 per cent. "apparently normal," the rest being too imperfectly reported to classify.

	Per Cent.
Reaction to galvanic and faradic both absent	4 = 4.9
Reaction to galvanic and faradic both diminished	40 = 48.8
Reaction to faradic absent	7 = 8.5
Reaction to faradic diminished	16 = 19.5
Reaction "myatonic in character"	1 = 1.2
	82.9

The reaction of degeneration was found only once, and here only "a few days before death."

I believe that the myatonic reaction will be found in every case of true amyotonia in which a careful examination of all the muscle groups is made by correct methods. It is, however, frequently present in differing degrees in different muscles in the same patient, and is often absent except in one or two groups of muscles.

The *intelligence* in amyotonia is usually normal. It was so found in 77.8 per cent. of the forty-five cases with notes on this point. That this is by no means a rule without exceptions is proved by the fact that 6.7 per cent. were said to be "backward," 4.4 per cent. were "impaired" mentally; that 2.2 per cent. were "dull," 4.4 per cent. "retarded," 2.2 per cent. idiotic, and 2.2 per cent. mongolian, making a total for deficient mentality of 22.2 per cent.

Abnormal mobility of the joints is one of the most constant symptoms of the disease, having been absent in only three of the fifty cases in which we have data on this point. It was found in the wrist five times, in the ankle four times, in the fingers, elbows and shoulders and hips each twice; in the knees once and in "all the joints" once. In the wrists the hypotonia is shown by the flail-like motion of the hands when the forearm is shaken, and in the feet by the extreme dorsiflexion which is possible. Data on the particular joints involved are decidedly incomplete.

Involvement of the heart muscle and of the involuntary muscle might be imagined as a possibility, but has never been reported. It was thought of in our case (J. C.) as a possible factor in the severe constipation with the formation of fecal impaction in the large intestine, but we finally came to the conclusion that the combination of extreme inactivity and hypotonia of the abdominal wall sufficiently explained the phenomenon. The blood pressure has been determined only in this one case (to my knowledge) and was slightly below normal (systolic 75). An electrocardiographic tracing was taken in this case also (Fig. 1), to determine the state of the heart muscle, with negative results.

Vasomotor disturbances are very infrequent. In one case marked dermographia was present and in another cold, blue extremities and frequent chilblains were recorded.

In two cases a firm edema of the face and extremities was found, and in one case the skin of the legs showed a marked thickening.

The *pad feet* described by Collier and Wilson as typical of the disease are rarely mentioned. They are well shown in the accompanying photograph (Fig. 5). *Flat feet,* resulting undoubtedly from the hypotonia of the calf muscles is mentioned twice and, judging by the frequency of involvement of the muscles of the calves and feet, occurred probably in more. *Contractures* were noted as present in 27 cases, or 81.8 per cent., and absent in 6 per cent. The hamstrings (noted as contracture of the knee, 5 times) are the most frequent seat of contractures, being mentioned no less than 10 times; next in frequency are the flexors of the thigh (5 times). The adductors of the thighs and the supinators of the forearm showed contracture in 3 cases. Contractures of the elbows, ankles, calves, and feet each occurred twice, and of the sternocleidomastoid and the biceps each once.

Special Senses.—Faulty *vision* and *hearing* were noted in one case, which also showed optic atrophy. The latter lesion was also found present in another instance. *Athetoid movements* are found twice noted, and "tremor" once. Athetoid movements are very readily confused with the physiologic movements of the hands in infancy. *Con-*

vulsions occurred four times, usually shortly before death, but sometimes as an event in early life. *Concomitant congenital defects* have been found in several cases and may be considered as affording corroboration of the theory of a developmental or germ plasm defect in the etiology of this disease. Congenital hernia occurred once, and congenital clubfoot three times. One patient had congenital (?) dislocations of the hip and thumb, and a malformation of the knee. A rudimentary penis associated with cryptorchidism was present in one case. Hemophilia was once noted.

Bones.—The bony changes which sometimes occur in amyotonia congenita usually appear to be secondary to hypotonia or due to lack of muscular support and activity. Thus, deformities of the chest were found eleven times. In one case the long bones were small and easily bent; in one case they were "atrophic," the femur being one half its normal size as shown by the Roentgen ray. In my case the bones showed medullary thinning with an apparent density of the cortex, like the changes in atrophy of disuse. In one case the Roentgen ray showed that the bones were "normal," but "undeveloped from want of use." Moderate evidences of rickets were found five times, a rather low figure considering the frequency of this disease in the hospital class of patients. *Malocclusion* of the jaws was twice noted.

Metabolism.—Gittings and Pemberton have published the results of metabolic experiments made on Griffith's patient. The creatinin excretion was found to be extremely low.

PROGNOSIS

Improvement was noted in 41 cases; merely as having occurred in 30, or 67.3 per cent. of these; as being slight in 6, and marked in 5. There was no improvement in 2 cases and 3 patients became worse. Improvement in this disease is, however, only relative. It is evident from a survey of the reported cases that a certain degree of improvement may be expected in nearly every case, but it should be remembered that no case of complete recovery has yet been reported and that there appears to be a limit in every case beyond which improvement does not go. In Oppenheim's last case the patient at the age of 12 years was undoubtedly worse than at the age of 4; he could walk only with difficulty, all the muscles were still weak and he suffered severely from flat-foot. This, with the exception of Hartenberg's extraordinary case seen at the age of 50 years, is the oldest one on record, a fact which may be in itself of significance.

Respiratory infection, evidently resulting from weak thoracic expansion, is the complication which is most to be feared and most carefully guarded against, as the mortality figures will show.

Mortality and Causes of Death.—Death occurred in thirty-six cases, making a mortality of 31.3 per cent. The cause of death is given in thirty instances as follows:

	Per Cent.
Pneumonia (usually bronchopneumonia)	24, or 80.0
Bronchitis	3, or 10.0
Diphtheria	1, or 3.3
"Convulsions"	1, or 3.3
"Acute fever"	1, or 3.3

Bronchitis in infants severe enough to cause death is usually complicated by involvement of the lung proper, so that pneumonia may be held to be responsible for 90 per cent. of the deaths in amyotonia congenita.

TREATMENT

No specific treatment is available. Epinephrin was tried once, and this case showed improvement. Concetti believes that thyroid extract is valuable, and two of his cases improved after its use, combined with massage, exercise, and electricity. Exercise, massage and stimulation of the affected muscles with the faradic current are the most effective measures. Medication with one or another of the preparations of strychnin and cod liver oil is serviceable. In view of the great danger of respiratory infection, it is extremely important to keep patients in the open air, to maintain nutrition and to avoid contact with persons suffering from any complaint of this kind. Exercise can be obtained by routine passive movements, and, perhaps more practically in many instances, by giving the younger patients toys heavy enough to require some muscular effort in handling, and in the case of older patients by carefully regulated manual work. It is most important to make these patients use the voluntary power which is present to some degree in practically all the muscles, in the hope of increasing it. Patients able to walk should be guarded against flatfoot by the use of properly constructed shoes giving support to the plantar arch.

I beg to acknowledge my indebtedness to the reviews of Collier and Wilson and of Griffith which have been freely used in compiling this paper. I wish to thank Dr. Walter F. Schaller for the electrical and general neurologic examinations of the new cases herewith reported, Dr. Roland Tupper for the electrocardiographic record of Case 3, and Dr. W. W. Boardman for the radiographic examinations.

CASE REPORTS FROM THE CHILDREN'S CLINIC OF STANFORD UNIVERSITY MEDICAL SCHOOL

Reports of the following cases from the Children's Clinic of Stanford University Medical School have not been previously published.

Case 1.—J. P., boy, aged 29 months; first seen Oct. 26, 1914; complaint, weakness.

Family History.—The parents have been married six years. The patient represents the third pregnancy. Within eight months before his conception the mother had two miscarriages.

Birth: Full term; instrumental delivery.

Patient's History.—He has always been weak. During the first week of life he had several convulsions, but none since that time. He was never breast fed. The first tooth was cut at 12 months. No paralysis was noticed until the mother tried to teach him to walk, when she found that the legs and back were weak and that he had difficulty in holding the head upright. He was late in learning to talk and his vocabulary is still limited to three or four words. Swallowing has been normal. He plays with his toys, using his hands with facility. He seems bright and affectionate, though easily excited. He has had none of the infectious diseases.

Examination.—There is no evidence of lues or rickets.

Head: Circumference 18.5 inches (47 cm.); oval; fontanel closed; pupils equal and react to light; no nystagmus; the eyes are slightly oblique; the teeth are normal in number, in good condition and well formed. The *hair* and *skin* are normal, without evidence of cretinism.

Muscular System: The muscles of the neck are relaxed and apparently unable to support the head properly. There is no atrophy, paralysis, spasticity, tremor or ataxia of the upper extremities, but there is some doubtful hypotonia of the fingers. He does not use the right hand voluntarily as much as the left. He grasps accurately. There is no atrophy, deformity or spasticity of the lower extremities, the muscular power of which seems to be normal in the reflex responses to stimulation. When he attempts to walk and stand there is apparent incoordination of the thighs with the trunk, the former flexing while the back goes into a flexed position with the head wobbling. He also shows a tendency to adduct the thighs when attempting to walk. He is able to take a few steps when the back is supported but otherwise cannot stand. He can sit alone but bends forward and there is pronounced weakness of the muscles of the back, so that the spine goes into a rounded kyphosis in its whole extent. There is no muscular spasm or other evidence of spinal tuberculosis.

Nervous System: The left knee-jerk is more pronounced than the right (?) but neither is exaggerated. Sensation is apparently normal throughout. The cranial nerves are normal in so far as they can be tested.

Electrical Reactions: The faradic response is relatively diminished in the deltoids, triceps muscles, erector spinae and the posterior cervical muscles. Elsewhere it is normal. The galvanic response shows a quantitative change in the deltoids and the anterior muscles of the legs. There is no reaction of degeneration.

CASE 2.—Baby N., boy, aged 8 weeks.

Family History.—The mother is 40 years old and is probably approaching the menopause, since before the present pregnancy began menstruation had been absent for several months. She has a funnel pelvis and a moderate degree of nephritis. This is her second pregnancy; the first, four years ago, terminated in an abortion at the second month. Her blood is negative to the Wassermann test.

Birth: Full term; birth weight 2,150 gm.; delivered by cesarean section; blood from the cord and from the heel gave a negative Wassermann reaction.

Patient's History.—This was uneventful, except for constipation, until the baby was 7 weeks old, when the father insisted that something was wrong with the left shoulder.

Examination.—The humeri are held at right angles with the body and the hands and forearms are in excessive pronation. All movements of the shoulder joints are possible and the elbow joints are normal. Supination in both lower arms is limited, whereas pronation can be carried out to an unusual extent.

The arms cannot be fully extended; when this is attempted, the tendon of the biceps muscles becomes tense.

The lower extremities are almost completely paralyzed, the left being specially flaccid. The hypotonicity of the muscles of the calf permits marked dorsiflexion of the foot.

Electrical Reactions: With the galvanic current, 1.5-2 m.a. give a normal reaction in the calf muscles, but no reaction at all can be obtained with the faradic. The thigh muscles on the right side react with 2.5 m.a., on the left with 4 m.a. The supinator longus reacts with 2.5 m.a. In general the muscles of the upper extremity react at about 2 m.a.

Case 3.—J. C., male, aged 30 months, was seen first, Sept. 30, 1916. Complaint: "Baby is like a bunch of rags."

Family History.—Father and mother are in good health; their ages are, respectively, 30 and 28 years. They have been married six years. There are no indications of tuberculosis or of syphilis. The first child died when one month of age, of unknown cause, and eight months later our patient was born. A third child, a boy, is now 18 months old and apparently normal.

Pregnancy: There were no prenatal disturbances. The mother does not remember whether or not she felt the prenatal movements.

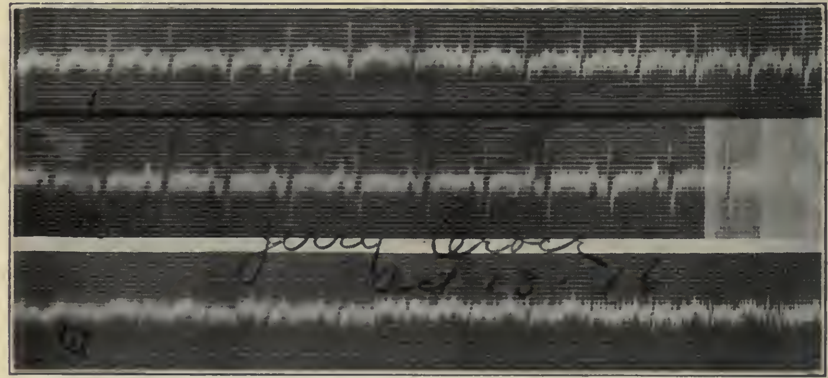

Fig. 1.—Electrocardiogram. Normal. Author's Case 3.

Birth: Born at full term. The labor was normal. The birth weight is not known.

Patient's History.—The patient was breast fed for 3 months, afterward on dilutions of cow's milk, and later on a rather careless general diet. The first tooth was cut at 6 months and the rest followed apparently at the usual intervals. The mother does not know when the anterior fontanel closed. About a year prior to being seen the boy had "pneumonia" which lasted twenty days and was followed by a good recovery. He has been obstinately constipated for the past year; he has enuresis; the mentality has been normal; at the age of 1 year he was able to speak a few words; his appetite is poor; he did not gain normally after the sixth month.

Present Illness.—His mother is sure that the weakness began at the time when she weaned the baby (at 3 months). Since then he has been weak and has never been able to sit up. He can, however, move the extremities voluntarily, though such efforts have always been weak.

Examination.—A rather poorly nourished male child, quiet and making few voluntary movements. The skin is soft and the hair fine.

Head: The anterior fontanel is closed. The suboccipito-bregmatic circumference is 47 cm. A very slight asymmetry of the skull is present, but there is no evidence of lues or rickets. The expression is decidedly inert, but when he cries there is no apparent paralysis or weakness. The action of the orbicularis oris and palpebrarum is strong. The muscles of the tongue and of the pharynx apparently act normally. There is no ptosis or strabismus.

The pupils react promptly to light. No nystagmus can be detected. Vision is probably good. The sclerae are bluish. There are no deformities of the ears, and hearing is normally acute. There are twenty-two teeth, all in good condition. There is marked malocclusion, the lower incisors lying in a vertical plane about ¼ inch posterior to that of the upper incisors. This deformity is apparently due to a shortening and broadening of the mandible. The palatal arch is normal. The tonsils are markedly enlarged, but not inflamed. The pharynx is normal. The tongue is protruded in the median line.

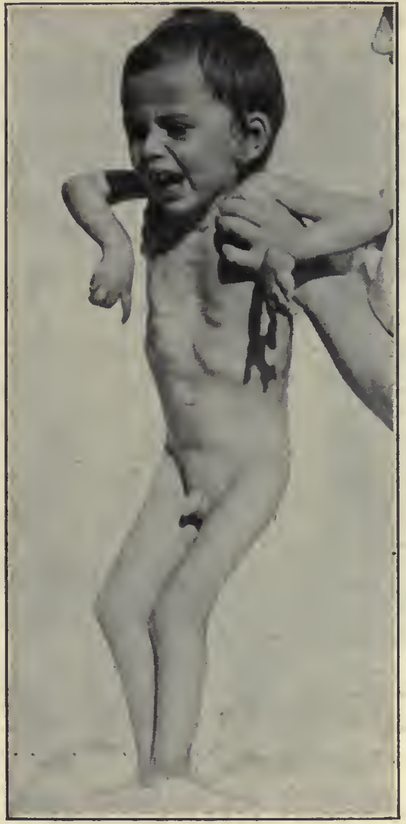

Fig. 2.—Case 3, showing weakness of shoulder muscles and deformity of thorax.

Neck: The thyroid is not palpable. The thymus cannot be felt in the suprasternal notch. Both the anterior and the posterior lymph glands are palpable.

Chest: The thorax presents a marked anteroposterior flattening, with the typical sternal depression of funnel-breast. There is no rosary, but the lower ribs flare slightly and there is a suggestion of Harrison's groove. The pectorales majores appear to be somewhat atrophic. On inspiration there is a definite retraction of the intercostal spaces and of the suprasternal notch. Respiration appears to be entirely abdominal. The only abnormalities found in the examination of the lungs are a few moist râles at the right base posteriorly and perhaps slight impairment of resonance at this point. (These signs were not again heard after the first examination). No thymus dulness can be elicited.

Back: When the patient is held in a sitting posture the entire spine shows a regular, evenly distributed kyphotic convexity, without lateral curvature, which disappears when he is laid on his back. There is no angular prominence, muscular spasm or other sign of spinal tuberculosis. The deformity is evidently due to weakness of the muscles.

Heart: Dulness is present from the right border of the sternum to the midclavicular line in the fourth space. The apex impulse is felt just below and about 1 cm. inside the same line. The rate varies considerably from time to time, but on the whole is normal. The first sound is somewhat shorter and sharper than usual, giving the impression of a lack of muscular tone. The second sound is normal. There are no murmurs or accentuations.

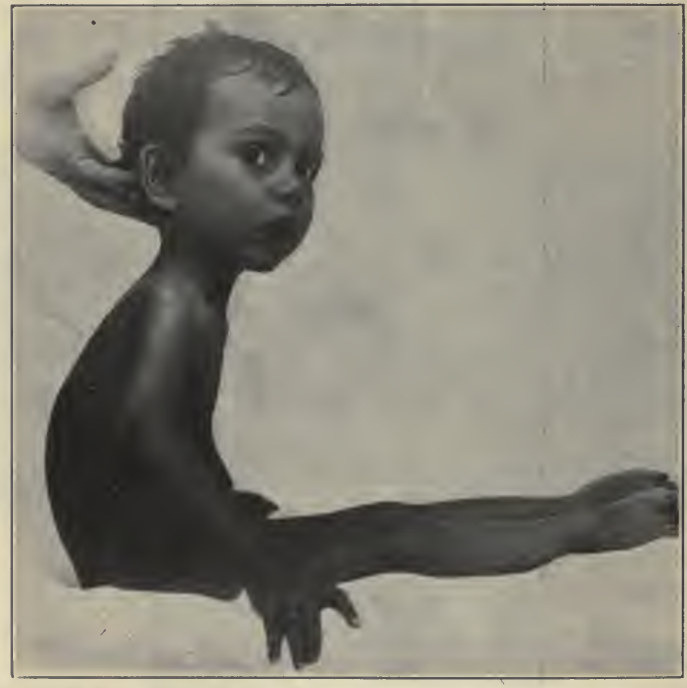

Fig. 3.—Case 3, showing weakness of back. The head has to be supported.

Abdomen: The circumference is 43.3 to 43.7 cm. with a maximum of 0.5 cm. The contour is rounded and quite normal. There are no signs of fluid. There are several hard, rounded masses which feel as if they were directly under the abdominal wall. Their outlines are sharp and distinct. One of these is a short distance above the symphysis and another in the region of the ascending colon. Several others are felt in various parts of the lower abdomen. There is no tenderness and no spasm, the abdominal wall being flaccid and toneless. The liver and the spleen are not palpable.

Lymph-Nodes: The inguinal and axillary glands are palpable, but small and discrete. The epitrochlears are not palpable.

Extremities: The great toes are held in rather sharp dorsiflexion. The feet are long, with peculiarly puffy plantar pads, which do not pit on pressure. The pads extend behind the os calcis, increasing the length of the foot considerably (Fig. 5). The metacarpo-phalangeal joint of the thumbs is very loose, admitting extreme hyperextension at this joint. The index finger of the right hand is constantly held in hyperextension nearly at right angles to the dorsum of the hand. The elbow joint can be slightly hyperextended and the wrists are so loose that the hands can be flapped to and fro like a flail. The hips are slightly hypermobile. The quadriceps femoris appears to be nearly powerless. The ankles permit dorsiflexion of the foot to an acute angle, but the dorsum of the foot cannot be approximated to the shin. The muscles throughout the body are soft. The upper arm muscles are small and probably atrophic, though no local wasting is apparent. The hands are long and gracile, with rather large hypothenar pads. The legs have the normal contour and are neither atrophic nor hypertrophic. All the muscles of the extremities feel soft, very much as though the soft parts consisted of fat. There is no fibrillation. The cervical muscles fail to support the head until it is lifted upright. When this is done the head does not drop, but is held unsteadily. There are no *contractures,* except possibly of the adductors of the thigh, which become taut when the legs are abducted (Fig. 6).

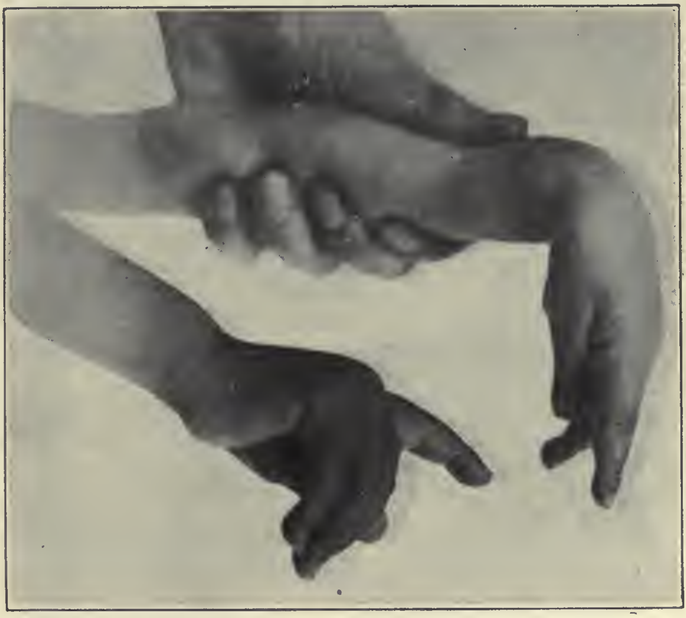

Fig. 4.—Case 3, showing weakness of extensors of left wrist, causing "flail wrist." The right wrist is much stronger.

Reflexes: No patellar, achilles, biceps, triceps, wrists, jaw or knee-jerks could be obtained. The upper abdominal reflexes are prompt, but the lower ones could not be obtained. The Babinski, Oppenheim and Gordon signs were positive.

Electrical Reactions: These were performed by Dr. Schaller who made the following note: "In the anterolateral group of the legs and in the muscles of the forearm the faradic response is perhaps somewhat, but not markedly, slowed. In the calf muscles and the thigh muscles the faradic response is markedly slowed. In the arm muscles proper, including the deltoid, there is a marked slowing of the contraction. By slowing is meant that a greater amount of current is required to produce a contraction. To the galvanic current the relative excitability of the muscles is the same as to the faradic current. There is no reaction of degeneration, but a diminished quantitative change. In general, hypoexcitability to both forms of current is more marked in the proximal than in the distal muscle groups. This electrical behavior is what would be expected in myatonia."

Urine: Specific gravity, 1.015; albumin, faint trace; sugar, none; casts, none; otherwise negative.

Blood (Oct. 11, 1916): Red blood cells, 5,064,000; hemoglobin, 85 per cent. (Sahli); color index, 0.85; white blood cells, 11,800; polymorphonuclears, 37 per cent.; lymphocytes, 60 per cent.; large mononuclears, 2 per cent.; eosinophils, 0; transitionals, 1 per cent.; (200 cells counted).

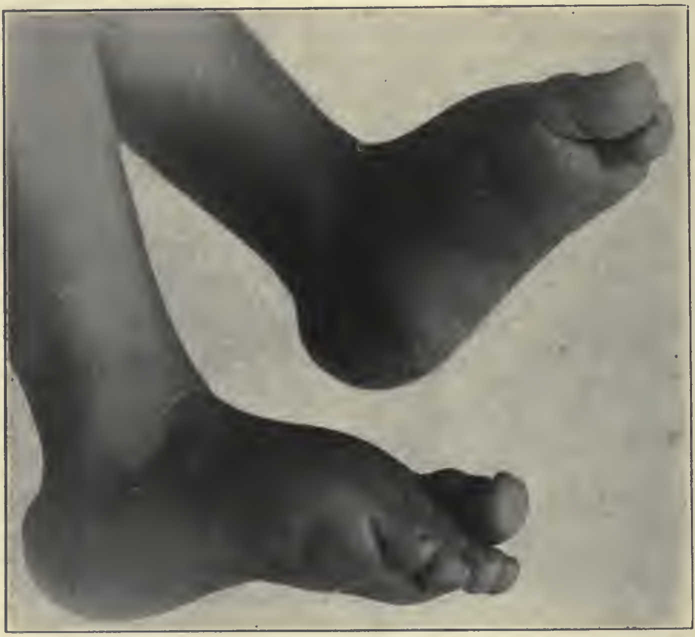

Fig. 5—Case 3, showing long, broad feet with marked increase of plantar subcutaneous tissue; so-called "pad feet."

Stool (Oct. 10): Small, fair consistency, greenish; considerable mucus and a small amount of blood; negative for formed elements. Wright stain shows many cocci and bacilli; no long chains, no pus cells. Sudan III shows excess of neutral fat; no fatty acids or soaps, by carbolfuchsin. Gram stain, shows gram-positive cocci in short chains, gram-positive and gram-negative cocci and bacilli. Lugol's iodin showed no starch.

A culture from the throat, taken as a routine precaution, was negative for diphtheria bacilli. The von Pirquet and Wassermann tests were negative.

The systolic blood pressure, taken Oct. 13, 1916, was 78 mm. (palpation); the diastolic could not be obtained.

An *electrocardiographic* tracing showed no abnormality.

Roentgenograms of the hands, forearms, thorax and spine, and of the legs were made by Dr. Boardman, who reported as follows:

"Examination shows no gross abnormalities in bony development. There is a medullary thinning of the long bones, with a resulting striking density in the cortex, giving the appearance of a penciled outline; this is especially seen in the short bones of the hand and is also seen in the carpal bones. There is no delay in the bony development as evidenced by the appearance of the centers of ossification. The whole picture is similar to that seen in the atrophy of disuse in adults, and I should be inclined to ascribe the appearance in this case to a similar process."

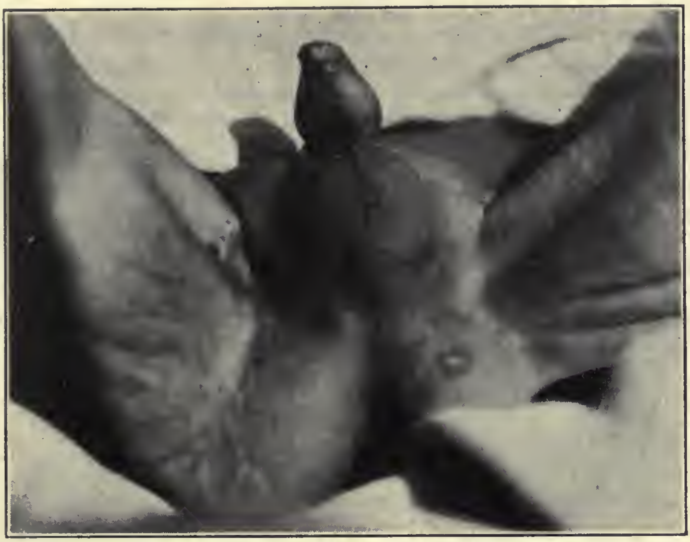

Fig. 6.—Case 3, showing retention of tonus in adductors of thighs.

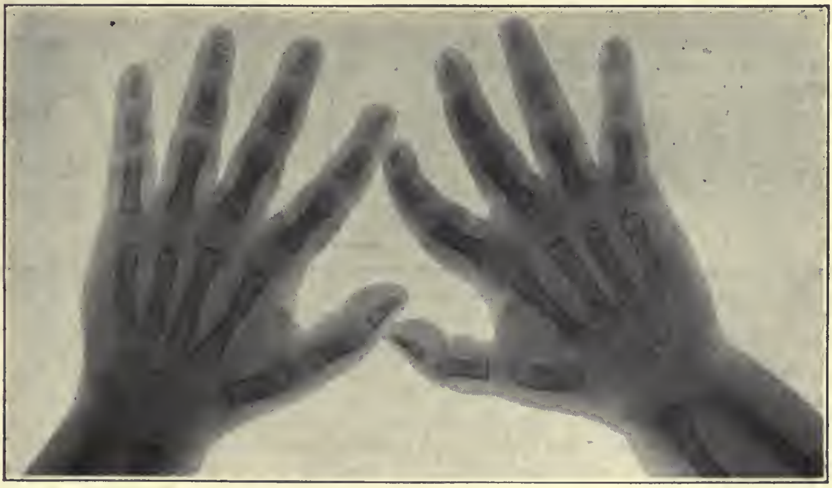

Fig. 7.—Case 3, radiograph showing rarefaction of the medulla and density of the cortex in the bones of the hand.

The abdominal masses, which had given rise to various diagnostic conjectures, disappeared after a series of soapsuds enemas. Scybalous masses, some of them as large as a hen's egg, very hard, of putty color and an extremely offensive putrefactive odor, were evacuated. A few days later the child developed a colitis with frequent passages of blood-stained mucus. This cleared up satisfactorily after a course of protein milk.

The condition of the musculature during the patient's short stay in the hospital remained stationary.

He has not yet been long enough under observation to permit any conclusions as to the progress of the disease.

ABSTRACTS OF CASES[3]

Zappert, O.—Boy, aged 6½ months. Onset at birth. Birth normal. Since birth has not been able to move legs. Great flaccidity of entire musculature. Cannot lift head. Arms somewhat elevated on shoulders, flexed at elbows, with the forearms in supination and the thumbs turned inwards. Legs motionless, feet in position of talipes equinus. Power of voluntary movement in arms very slight and almost absent in fingers. Tendon reflexes completely absent. Abdominal reflex absent. Abdomen distended. Respiration mainly abdominal. Paralysis of extremities somewhat more marked on right side than on left.

(Zappert leaves diagnosis undecided, but does not believe it to be poliomyelitis. This case, to which attention was called by Rothmann, seems so typical of amyotonia that I have included it in the series.)

Bernhardt, M.—Boy, aged 9 months. Premature; birth weight less than 3 pounds. Onset at fourth month. No involvement of face. Extremities weak. No response to faradic; to galvanic much diminished. Superficial and tendon reflexes not noted. Back shows kyphoscoliosis. Hypermobility present. Neck muscles weak. Unusual only in fact of prematurity.

Archangelsky, W., and Abrikosoff, A.—Girl, aged 3½ months. Onset probably at birth. Quickening present, but weak. Involvement of muscles of neck, upper and lower extremities, and trunk. Doubtful contracture of biceps. Knee-jerks absent. No response to faradic current, except in facial muscles. Marked deformity of chest. Breathing almost entirely abdominal. Abdomen distended. Marked hyperextension. Sensation normal. Birth weight 8½ pounds. Died of pneumonia. Necropsy.

Carcupino Ferrari, D.—Girl, aged 3½ months. Family history, pregnancy and birth normal. Quickening at the fourth month. At birth, weakness of all muscles including those of the neck. Active movements lacking except under strong electrical stimulation. Plantar and patellar reflexes diminished, abdominal uncertain, pharyngeal and pupillary normal. Pain and thermal sense normal. Slight improvement in two months. The baby then died of bronchopneumonia. During the last days of life there was a complete reaction of degeneration in some muscles and an incomplete in others.

Concetti, L.—1. Boy, aged 1½ months. Onset at birth. The parents are 58 and 50 years old. Quickening noted but not active. Muscle tone very deficient in all the extremities which are flaccid and permit free movement in all directions. Legs motionless. Arms in exaggerated supination and held away from trunk. Some voluntary movements of fingers and hands. Cannot sit up. Marked kyphosis. Head falls in all directions. Respiration entirely abdominal with retraction of epigastrium and suprasternal space. Abdominal muscles weak. In the face the folds are not normally distinct and there is an expression of indifference. Muscles of deglutition and of the eyes normal. Knee-jerks absent. Electrical excitability much diminished. No reaction of degeneration. Mentality normal. Marked improvement on massage and electricity. Died several months later of bronchopneumonia.

2. Boy, aged, 7 months. Second child. The first was premature and died two hours after birth. At the sixth month of pregnancy the mother noticed

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[3] Excluding the three cases reported in full elsewhere in this paper, and the sixty cases reviewed by Griffith, the references to which will be found in the bibliography.

that the fetal movements disappeared, returning at the eighth month, but feebly. Difficult labor. Born asphyxiated.

Infant small but with excessive fat deposit on legs and firm edema. Flaccid and relaxed and fell in a heap because of relaxation of muscles and joints. Some voluntary movements of the hands at two months. Examined by Concetti at the age of 7 months. Head dangles in all directions. Trunk goes into marked dorsal kyphosis when sitting. All the extremities flaccid, though some motions of the hands, forearms, and toes are made and there is some resistance in the abductors of the thighs. Muscles of face, eyes, and of deglutition normal. Sensation normal. Tendon reflexes absent. No atrophy. No reaction of degeneration. Testes undescended and penis rudimentary. Mentally a little below normal. Remarkable improvement on electricity, massage and thyroid extract. Died some time later of bronchopneumonia.

3. Girl, aged 8 months. Onset at birth. Family history negative. During last week of pregnancy mother noticed a progressive weakening of the fetal movements. Normal birth. Infant very small. The entire body was relaxed, the head falling in every direction, the trunks and legs flaccid, the legs motionless. Hypermobility of all joints. Voice feeble.

Seen by Concetti at 4 months. Head small with frontal and parietal bosses. Mongolian facies. Eyes oblique and almond shaped. Excessive adipose deposit and general pseudo-edema. On lower extremities and over deltoids and in supraclavicular region there are soft, elastic fat pads. Indifferent to surroundings. Does not smile. Movements of mastication normal. Muscles flaccid, not atrophic. Tendon reflexes absent. Rosary present. Large, flaccid abdomen. Marked improvement on thyroid with disappearance of pseudo-edema and fat pads and improvement of mentality (doubtful case).

4. Girl. (Patient not seen by Concetti. History obtained from parents). First child of young and healthy parents. Born in a state of flaccid immobility of all limbs. Sucked well and was abnormally fat. Died at age of 3 months of bronchopneumonia. Shortly before death she showed slight movements of the hands. (Data insufficient for definite diagnosis.)

5. Boy, aged 2 months. Brother of patient, Case 4. Quickening became weak during last month of pregnancy. Muscular flaccidity of extremities, neck, and back. Diminished thoracic expansion. Firm edema of calves, lower half of thigh and of forearms. Face a little apathetic. Sucks well. Well nourished. Weight 4,650 gm. Body length 54 cm. Improved on massage and thyroid extract. Died at age of 5 months of bronchopneumonia.

6. Boy, aged 6 months. No hereditary taint. Born flaccid and asthenic. Complete immobility of lower limbs. Condition less marked in upper extremities. Limited movements possible in forearms and hands. Trunk curved forward when sitting. Head well supported on shoulders. Reflexes absent. Muscles not atrophic but lacking in tone. Intelligence retarded. Subcutaneous fat abundant. The fetal movements were always weak, especially during the last month of pregnancy.

7. Girl, aged 4½ months. Parents young and robust. Immobility first noticed at 2 months (but parents could not say that he had moved since birth). Flaccidity of muscles of neck and back. "The signs of hypothyroidism were evident." Abdomen large and flaccid with a large umbilical hernia. There was never any attempt at laughing and very little at crying. Firm edema of calves, feet, and external side of thighs. Skin rough. Hair fine, stiff and dry. Constipapated. (Examination was not completed and the patient was lost sight of.) She died a few months later of bronchopneumonia.

Councilman, W. T., and Dunn, C. H.—Boy, aged 6 months. Onset at 3 weeks. Quickening present and normal. Involvement of upper and lower extremities, trunk and neck. No involvement of face. No contractures. Knee-jerks absent. Electrical reactions not performed. Deformities of chest. Respiration abdominal. Died. Necropsy.

Rietschl.—Sex not stated; 4 years old. Onset at birth. Improvement after treatment with faradic current (further details not given).

Schippers, J. C.—Boy, aged 2 years. Onset at birth. Main involvement in buttocks and extremities. Muscles of face, deglutition and mastication normal. Faradic and galvanic response diminished. No reaction of degeneration. Athetoid movements of fingers and toes. Marked dermographia. Babinski positive. Wassermann and von Pirquet negative. Gradual improvement after eight months.

Batten, F. E.—Boy, aged 6 years. Onset at birth (?). Involvement of muscles of upper and lower extremities and trunk. No involvement of facial muscles. Knee-jerks present. Faradic response diminished. Galvanic not noted. Marked spinal lordosis. Hypermobility of feet and hands. Sensation normal. No contractures. Improvement doubtful.

Beling, C. C.—Boy, aged 3 years. Onset at birth. Involvement of muscles of neck, upper and lower extremities, and trunk. No contractures. Wrist and elbow jerks present, knee-jerks absent. Electrical reactions "myatonic in character." Head circumference 20⅛ inches; chest circumference 29 inches. Harrison's groove. Abdomen 30 inches, protuberant. Back: marked weakness and kyphoscoliosis. Hypermobility present. Sensation: touch normal; pain sense diminished (?). Wassermann negative. Mentality normal. Improvement.

Charles, J. R.—Boy, aged 6 years. Onset at birth. Quickening felt. Involvement of arms, legs, and trunk. No involvement of muscles supplied by cranial nerves. Knee-jerks present. Triceps jerk absent. Wrist jerk present. No Babinski. Sensation normal. Faradic response diminished "in some" muscles. Flail wrists, knees, and ankles. Flat foot. Partial dislocation of wrist joints. Mentality normal. Double congenital inguinal hernia. Began to walk and talk at 2 years.

Duthoit, R.—Girl, aged 2 years. Onset at birth. Quickening at fifth month. Involvement of muscles of upper and lower extremities and trunk. No involvement of face. Tendon reflexes absent. Electrical reactions: faradic response diminished and sluggish; galvanic diminished but prompt. Involvement of intercostal muscles. Kyphosis. Hypermobility of all joints. Sensation normal. Improvement on thyroid extract.

Feer, E.—Girl, aged 4½ months. Onset at birth. Quickening noted. Involvement of muscles of upper and lower extremities and neck. No involvement of face. Tendon reflexes absent. Superficial reactions present. Faradic response diminished and sluggish. Galvanic diminished. Slight improvement. Harrison's groove present. Respiration abdominal. Abdomen very soft. Hypermobility present. Mentality normal.

Guinon and Gaudncheau.—(Doubtful case.) Family history negative. Birth normal. Extreme weakness of musculature and apparently complete absence of motion. Extreme lordosis. Head in opisthotonos. Lower jaw dislocated. Slight stiffness of muscles followed by flaccidity when child was moved. Respiration abdominal. Muscles of face and pharynx uninvolved. Ptosis, nystagmus, and strabismus. Apparent deafness. Tendon reflexes absent. Skin reflexes lively. Sensation normal. No fibrillary twitchings. Electrical reactions normal.

Marburg, O.—1. Boy, aged 3 months. Onset at six weeks. Pregnancy normal. Patient was seventh child. Birth weight 3,740 gm. Involvement mainly of neck, arms and legs. Trichterbrust. Contracture of arms at elbow. Knee-jerks and abdominal reflex absent. Mentality apparently normal. Died of bronchopneumonia.

2. Girl, aged 6 years. Onset at birth. During pregnancy mother had vomiting and loss of appetite. Patient had rickets, and scarlet fever at 3 years. Involvement of arms, shoulder girdle and legs. Face and neck not involved. Contractures of elbows, ankles and adductors of the thigh. Hammer toe. Hyperextension of shoulder, wrist, and fingers. Spinal muscles not involved.

Triceps and knee-jerks absent. Sensation normal, Superficial reflexes present. Electrical responses quantitatively diminished.

Mensi, E.—1. Girl, aged 12 days. Weight 2,090 gm. Icterus. Cephalhematoma. Arms inert at side of body. Slight flexure of forearms and arm and of last four fingers. Passive movements free. No atrophy. Died of bronchopneumonia.

2. Boy, aged 4 days. Weight 2,750 gm. Edema of feet and legs. Paresis of extensors of hands. Lower extremities completely immobile; when picked up they fall inert. No spasm or atrophy. Died at 27 days of bronchopneumonia.

3. Boy, aged 2 days. Weight 2,800 gm. Complete immobility of lower extremities. Some slight movements of upper extremities and head. Joints loose. No hypertonic spasm or atrophy. Died at 2 months of bronchopneumonia.

4. Girl, aged 1½ months. Weight 2,800 gm. Immobility of upper extremities, especially left. Paresis of extensors of hand. Immobility of lower limbs. Knee-jerks absent. Plantar reflex present. Passive movements free in all joints. No spasm or atrophy. Cutaneous edema of forearms and legs. Died of bronchopneumonia.

5. Girl. Seen at birth. Weight 1,600 gm. Atony of upper extremities. When picked up the arm falls without tone. Slight movements of rotation of arm, of abduction of hand and of the shoulder, and of flexion of the forearm at the elbow. The head wobbles in all directions. The lower limbs also move, but weakly. Plantar and patellar reflexes present. No atrophy. Died at the age of 3 weeks of bronchopneumonia.

Oppenheim, H.—Boy, aged 12 years. Onset at birth. Never able to hold up head or sit erect. Late in learning to walk; then only with support. Condition stationary to the third or fourth year, after which he gradually became worse. Mentality normal. Muscles supplied by cranial nerves normal. Main involvement in legs with marked hypotonia. Contractures of flexors of knee, latissimus dorsi and biceps. Weakness in all muscle groups. Arms weak and hypotonic. Neck slightly weak. Electrical reactions show quantitative decrease. No reaction of degeneration. Abdominal reflexes absent. Sensation normal.

Snow, I. M.—Boy, aged 2 years and 9 months. One older brother mentally backward. At the age of 2 months had an illness characterized by fever, unconsciousness and retraction of the head, and anesthesia of the legs. No convulsions. Following this, the legs were tender for three weeks, and ever since they have been weak. At the age of 2 years patient could feed himself and sit erect, but the legs were weak. No absolute paralysis. Knee-jerks absent. Babinski positive. Faradic and galvanic response in all the leg muscles; sluggish in the abductors. Hypermobility of legs. No atrophy. (Case anomalous in onset, distribution, and electrical reaction.)

Thorspecken, O.—Girl, aged 4½ years. Date of onset not known. Quickening present. Involvement of muscles of neck, trunk and legs. Face not involved. Contractures of foot. Hypermobility of hips. Deformity of chest. Weakness of abdominal wall. Kyphoscoliosis. Tendon reflexes absent. Sensation, when patient was first seen, diminished; later, normal. Upper abdominal reflex present; lower, absent. Electrical reactions: faradic much diminished. Mentality normal. Wassermann negative. Roentgen ray shows atrophy of long bones, femur being one-half normal diameter. Improvement on exercise and faradization.

Bienfait.—Boy, aged 12 months. Weight 10½ kilos. Onset at birth. No voluntary movements until recently. There is now some action of extremities. Cannot sit up. Face and hearing normal. Mentality backward. Tendon reflexes weak. Abdominal reflexes absent. Improvement beginning after treatment with massage and electricity.

Concetti, L.—1. Girl, aged 3 years. Mother alcoholic. Normal pregnancy and birth. Onset at birth. Lower extremities immobile and atonic. The upper also appeared weak with limited powers of motion. For the past year she has tried to walk but falls "like a rag." General hypotonia and flaccidity of muscles, especially of the legs. All joints relaxed. Dorsal kyphosis. Knee-jerks present but torpid. Plantar reflex flexor in type. Faradic and galvanic response both diminished. No reaction of degeneration. Constipated. Intelligence a little retarded. Some improvement after treatment with massage and electricity.

2. Girl, aged 53 days. Family history negative. The fetal movements near term were feeble. At 4 days of age it was noticed that the lower extremities were inert and that the upper were held in supination, with slight movements of the fingers and hands. No resistance to passive movements. Joints relaxed. When sitting there is a large dorsolumbar kyphosis and the head falls of its own weight. When the child is lifted by the axillae the head and neck fall on the shoulders. Tendon reflexes absent. Thorax deformed, with lateral depressions and prominence of the sternum. Abdomen large. Spleen palpable. Respiration weak and mainly abdominal. Movements of suction, deglutition, and expression and of the eyes normal. Electrical excitability diminished. No reaction of degeneration. Died at the age of 2 months of bronchopneumonia.

Cotterill.—Girl, aged 2½ years. Onset at birth. Involvement of face, neck, trunk, upper extremities, and especially lower extremities. Contracture of sternocleidomastoid muscle. Knee jerks absent. Abdominal muscles weak. Umbilical hernia. Kyphoscoliosis. Hyperextension. Sensation normal. Superficial reactions absent. Dislocation of right hip. Malformation of right knee. Partial luxation of left thumb. Gradual improvement.

Fletcher, H. M.—Boy, aged 3 years. Onset at birth. Face "expressionless." Involvement of upper and lower extremities and trunk. Hypermobility very marked. Contractures of the hamstrings. Knee-jerks "very difficult to obtain." Electrical reactions: faradic and galvanic both diminished. Superficial reactions present. Mentality normal. Wassermann negative.

Foot, N. C.—Boy, aged 3½ months. Onset at birth. Quickening noticed, but feeble. Involvement of upper and lower extremities. Knee-jerks present but diminished. Electrical reactions diminished. Respiration mainly abdominal. Abdomen tympanitic. Died. Necropsy.

Gatti, L.—Aged 3 years. Onset at birth. Flaccid paralysis of the lower extremities. Marked muscular atony. Feet plump and flat. Reflexes and electrical irritability retained. Improved.

Gordon, A.—Two cases not reported separately. Weak muscular tonus. Paretic condition of limbs and trunk, dating from birth. Loss of reflexes. Weak response to faradism and galvanism. One case shows double optic atrophy and positive Wassermann. Both unable to sit erect, but have shown improvement. In discussion, Spiller thought one case not myatonia congenita; but Gordon reasserted his diagnosis.

Hertz, A. F., and Johnson, W.—Boy, aged 3½ years. Onset at birth. Face not involved. Upper and lower extremities, trunk and neck involved. Tendon reflexes absent. Scoliosis. Hypermobility. Mentality normal. Improvement: a little stronger than two years ago.

Kaumheimer, L.—Girl, aged 3¾ months. Onset at birth. Quickening noted. Involvement of neck, upper extremities, lower extremities, and trunk. Contractures present. Tendon reflexes absent. Electrical reactions: faradic much diminished, galvanic weak. Head, circumference 41 cm. Thorax deformed; thoracic respiration poor. Abdomen protuberant. Kyphosis. Hypermobility present. Small at birth. Wassermann negative. Von Pirquet negative. Died.

Koch, George.—Child aged 1¼ years. Sex not stated. Onset at 6 months. Quickening noted. Involvement of neck, upper and lower extremities and trunk; face not involved. Knee-jerks present but diminished. Electrical reactions: faradic and galvanic both diminished, but galvanic more. Hypermobility present. Superficial reactions absent. Mentality normal. Nystagmus present.

Reiner, H.—1. Girl, aged 3 years. Involvement of upper (?) and lower extremities and trunk. Tendon reflexes absent. Electrical reactions: faradic diminished but prompt; galvanic diminished. Sensation normal. Superficial reactions present. Mentality normal. One of twins, the other dying intrapartum. Improvement was marked after two months.

2. Boy, aged 11 months. Onset at birth (?). Involvement of trunk and lower extremities. Tendon reflexes diminished. Electrical reactions: faradic and galvanic response both diminished. Sensation normal. Superficial reactions present. Hypermobility present.

Collier, J.—Boy, aged 5 years. Involvement of lower extremities. Tendon reflexes "difficult to obtain." Electrical reactions: faradic diminished. Hypermobility in ankles. Improved on rest and exercises.

Courtney, J. W., and Eaton, H. B.—Boy, aged 5½ years. Onset at birth. Quickening present. Speech defective. Drools. Involvement of trunk. Tendon reflexes absent. Electrical reactions: faradic normal (six weeks after first seen). Superficial reactions sluggish. Mentality normal. Circumference of head 53 cm. Patient was a 7-months premature baby. Improvement. After six weeks, knee-jerks and achilles jerks were present.

Dunn, C. H.—1. Boy, aged 5 months. Onset at birth. Quickening present but diminished. Face not involved. Involvement of upper and lower extremities, neck, and pectoral muscles. Tendon reflex absent. Electrical reactions not noted. Breathing abdominal. Died of bronchopneumonia.

2. Girl, aged 5 months. Onset at birth. Quickening present but faint. Involvement of muscles of deglutition, neck, and lower and upper extremities. Chest deformed. Involvement of muscles of shoulder girdle. Knee-jerks absent. Electrical reactions not noted. Died of bronchopneumonia.

Purser, F. C.—Boy, aged 2¼ years. Onset at birth. Quickening noted. Face not involved. Upper extremities and trunk, and especially lower extremities involved. Tendon reflexes absent, except that knee-jerks can be obtained at rare intervals. Electrical reactions: faradic diminished. Hypermobility. Sensation normal. Superficial reactions present. Nystagmus. Tremor. Mentality "average." Improved greatly.

Skoog, A. L.—1. Boy, aged 6 years. Onset at birth. Quickening absent. Involvement of muscles of face, neck, upper and lower extremities, and trunk. Tendon reflexes absent. Electrical reactions: response to faradic and galvanic current diminished. Hypermobility present. Sensation normal. Superficial reactions present. Wassermann negative. Spinal fluid negative. Mentality normal by the Binet tests. Improvement.

2. Brother of preceding. Boy, aged 4 years. Onset early in first year. Involvement of upper and lower extremities. Tendon reflexes negative. Wassermann negative. Spinal fluid negative. Mentality normal. Improved, regaining greater part of muscular activity. Muscle biopsy.

Strauch, A.—Girl, aged 3 months. Second child. Onset during second week. Action of facial muscles fairly strong but unless aroused, few facial movements are made. Nystagmus. Involvement of muscles of neck, arms, trunk, and legs. Respiration abdominal. Abdomen prominent and tympanitic. Constipated. All tendon reflexes absent except for a doubtful biceps jerk. Superficial reflexes absent. Electrical reactions: faradic absent; galvanic diminished but prompt. No sensory disturbance. Slight tendency to improvement during first month of observation, then stationary. Died of unknown cause at 5 months.

Sutherland, G. A.—Boy, aged 2 years. No involvement of face or trunk. Lower extremities involved. Knee-jerks absent. Electrical reactions not stated. Dilatation of colon with large fecal impaction. Foul stools. Hypermobility present. Mentality backward (?). Improvement in abdominal condition.

ABSTRACTS OF NECROPSIES

Spiller.—Aged 22 months. Muscles pale and flabby. Fibers small. Transverse striation well preserved; longitudinal not so distinct. Fatty infiltration and increase of connective tissue in which the nuclei are increased in number. No degeneration of the peripheral nerves, and the anterior and posterior roots are normal. Anterior horns normal, also the cord tracts and the cerebrum and cerebellum, with the exception of the paracentral lobules, in which the Betz cells are not normally numerous. Heart and thymus normal. Rigor mortis absent.

Baudouin.—Aged 4 months. Muscle fibers mostly small with some hypertrophied fibers. Anterior roots small (one-half normal size). Cells of the anterior horns small and probably reduced in number. Sclerosis of the thymus and of the thyroid.

Reyher and Helmholz.—Age not stated. No clinical details. Muscle fibers of various sizes, some thinner and some broader than normal. Transverse striations indistinct or absent and the longitudinal in some parts appear to be lost. Muscles infiltrated with fat and a very cellular connective tissue.

Collier and Holmes.—Aged 7 years. Muscles small and pale, except the diaphragm which is normal. A few hypertrophied fibers. Transverse striations distinct and the longitudinal "unduly" distinct. Great proliferation of the sarcolemma nuclei. Vacuolation of some fibers. Connective tissue and fat greatly increased. Peripheral nerves poorly myelinated. Anterior roots very slender; posterior normal. In the anterior horns the motor cells are only about one-third the normal number. Dorsal horns and Clarke's column normal. Thymus and thyroid normal.

Lereboullet and Baudouin.—Aged 15 months. Some muscle fibers small, some very large. Transverse striations have disappeared, but the longitudinal are distinct. Great proliferation of the sarcolemma nuclei. Connective tissue increased. Anterior and posterior roots normal. No diminution in volume and no degeneration in the anterior horns. The brain is normal. Thymus, thyroid, and adrenals normal.

Rothmann.—Aged 5 months. (Case reported clinically by Haberman.) Muscles pale. Size of fibers not noted. Many have disappeared. Transverse striations distinct. Marked increase of the fatty tissue and connective tissue, the latter rather cellular. No degeneration in the peripheral nerves, but a marked increase in the connective tissue; nerve fibers small, but with a distinct medullary sheath. Anterior roots small and a large proportion of the fibers lack medullary sheaths. Posterior roots normal except in the lumbar region where they are atrophic. In anterior horns, cells very much diminished in number and the large ganglion cells absent. In the dorsal segments the posterior cells also fewer than normal. The large cells also absent in Clarke's column, and minor changes in the anterolateral tracts. The hypoglossus nucleus also shows a diminution in the number of cells and chromatolysis is noted in those present. No degeneration in the cord or the spinal roots. A notable feature of this necropsy is the examination of the nerve-endings in the muscles. It was found that the entrance of the nerves into the muscle fibers could be seen but that the end-plates were absent. In the cord, the glia is increased, as apparently is the number of vessels, the latter having thickened walls without intimal changes. Some perivascular hemorrhages in the cord. Cerebellum small. Heart normal. Thymus very large, with thickening of the walls of the vessels. Rigor mortis absent.

Pollak.—The details of this necropsy have never been published. Thymus larger than normal. Thyroid large.

Archangelsky and Abrikosoff.—Aged 7 months. Muscles pale and flabby excepting the diaphragm and the muscles of tongue and pharynx. Fibers very small; some hypertrophied fibers. Transverse and longitudinal striations distinct. No increase of sarcolemma nuclei, fat or connective tissue. Cohnheim's fields normal. Nerve endings normal. In the peripheral nerves one-third to one-half of the fibers are not myelinated. No degeneration. The anterior roots are only about one-fourth the size of the posterior, and only about one-half of the fibers are myelinated. Posterior roots and their fibers normal. Cells of anterior horns very few and small; those in the posterior horn larger. Some slight changes in the staining properties of Gower's and the pyramidal tracts without evidence of degeneration. No change in the neuroglia. In the cord many fibers are not myelinated, and even those which are, seem to be smaller than normal. Rigor mortis absent. Embryonal fatty tissue present around the kidneys. Nerve-endings in muscles present (no statement as to end plates).

Berghinz.—(No clinical details. Doubtful case.) Cells of anterior horns small and few. Nerve cells of cerebellum small. Hypoplasia and microgyria of the cerebrum. Glands of internal secretion normal.

Councilman and Dunn.—Aged 7½ months. Muscles small, flabby, grayish and translucent, excepting the diaphragm, which is normal. Many of the fibers small, the larger ones being of normal size. Transverse and longitudinal striations present in most fibers, but absent in some. No actual increase in sarcolemma nuclei, but these appear numerous because of the small size of the muscle fibers. No fatty degeneration. In the affected muscles the peripheral nerves lack myelin and some are degenerated. The fibers in the roots of the cord are normal. There is no apparent reduction in number of the cells of the gray matter in the cord. Neuroglia normal. No nerve-endings are found in the affected muscles. Heart, blood vessels and adrenals normal. Thymus large (29.2 gm.). Thyroid small. Rigor mortis absent.

Griffith and Spiller.—Aged 25 months. Muscles pale, soft, flabby. Most muscle fibers small; a few hypertrophic. Transverse striations distinct; longitudinal not distinct. Sarcolemma nuclei "excessive" in number. Some muscle fibers are vacuolated and give the reaction for fat. Connective tissue increased. Marked degeneration in the posterior tibial nerve, not in the median. Anterior roots small, with degeneration in the seventh and eighth cervical. Posterior roots normal. The cells of the anterior horns very few and small. Clarke's column normal. Brain very large (1,542 gm.). Pia of the cord edematous. Blood vessels normal except in the calf muscles, where they are much sclerosed. Heart pale, yellowish gray, and of good consistency, but the papillary muscles are pale and short. Heart muscle shows distinct cross striation, but there is a good deal of polar pigment. Thymus small. Thyroid small. Adrenals small, pale, yellowish, and show absence of chromaffinic cells.

Mensi.—(Five cases reported together.) Ages 1 day to 1½ months. Muscle fibers and bundles slender. Cross striations absent or indistinct. No nerve-endings can be found. Anterior horn cells reduced in number and are prevailingly multipolar, with the large ganglion cells absent.

Marburg.—Aged 3 months. Fibers in part very small and in part of larger—probably normal—size. Transverse striation present except in the very smallest; longitudinal also distinct. Sarcolemma nuclei only apparently increased by contrast with the smallness of the muscle fibers. Replacement of the muscle by fat and connective tissue. In peripheral nerves no degeneration but fewer fibers than normal and these deficient in myelin; connective tissue increase. Deficient myelinization of the anterior roots; posterior roots normal. The cells of the anterior horns are few, small, and pyknotic. Cells of posterior horns and of Clarke's column normal. Fibers of the cord tracts deficient in myelin. There is a connective tissue and neuroglia increase in the cord and the vessels have thickened walls. Thymus, thyroid and adrenals normal.

Concetti.—Aged 53 days. Muscles soft and pale. Muscle fibers: some small, some normal, some hypertrophic. Transverse and longitudinal striations normal. Sarcolemma nuclei not increased. No increase of connective tissue. No hyaloid fibers. In the peripheral nerves a few fibers lack myelin but there is no degeneration. The anterior roots are a little smaller than normal. Anterior horn cells very few and very small. Large ganglion cells absent. Cells fusiform and pyknotic. Clarke's column and the pyramidal tracts normal. In the cerebellum the Purkinje cells are few and altered in shape. All layers of the cerebrum reduced in volume. Glia normal.

Foot.—Aged 3½ months. Muscles pale, resembling raw pork. Muscle fibers: some very small, some moderately small, some normal. Transverse and longitudinal striations present. Sarcolemma nuclei not increased. Connective tissue not increased. Fatty changes in some fibers and some fibers are hyaloid. Some areas of round cell infiltration in the rectus abdominis. The peripheral nerves show very defective myelinization. Cells of the anterior horns reduced in number and size. Some are vacuolated and many are misshapen. The tracts, excepting the posterior and the direct cerebellar, are pale, showing deficient myelinization. Normal nerve endings in normal fibers, but none in the small fibers. Marked gliosis in the anterior horns. Cerebrum normal. Heart, thymus, thyroid and adrenals normal.

Kaumheimer.—Aged 4 months. Muscles pale and thin. Many small muscle fibers and some hypertrophic. Transverse striations distinct except in hypertrophied fibers. The fibers contain abundant nuclei. Increase in the fat and connective tissue. In the peripheral nerves, the number of fibers is diminished and there is an increase in the connective tissue, but no axis cylinders without medullary sheaths are found. Schwann's nuclei increased. Anterior roots small. Cells of anterior horns few, small, misshapen and pyknotic; in some places only cell shadows remain. In tracts some degenerated fibers but none deficient in myelin. Cells in Clarke's column show changes similar to those in the anterior horns, as do those in the hypoglossus nucleus which appear to be severely involved. Patchy gliosis in the cord, and some large "neurophage" cells. No evidence of an inflammatory process. Rigor mortis absent except in the lower jaw.

Strauch.—Aged 3 months. (Muscle only examined.) Muscle pinkish. Fibers small, of various sizes. No hypertrophic fibers. Transverse striations less distinct than normal; longitudinal indistinct. Enormous increase of sarcolemma nuclei with mitotic figures, indicating regeneration. One third to one half of the muscle consists of areolar tissue. The nerves in the muscle are slightly deficient in myelin and show an increase of the connective tissue.

MUSCLE BIOPSIES

Bing.—Aged 3½ years. No abnormalities except an increase in nuclei.

Collier and Holmes.—Aged 3½ years. Muscles pale, fatty, with little muscle tissue visible. Fibers very small excepting many hypertrophic fibers. Transverse striations distinct, also longitudinal. Great proliferation of the sarcolemma nuclei. Connective tissue increased. Nerve fibers poorly myelinated. Thickening of vessel walls due to a periarteritis with foci of small cells at intervals. Some intimal proliferation.

Openshaw.—Aged 7½ years. Hamstrings tough and fibrous. Vastus internus anemic and yellowish. Transverse striations absent. Fatty infiltration and "signs of regeneration" are noted.

Skoog.—Aged 22 months. Muscle pale. Fibers small, none hypertrophied. Transverse striations lost. Sarcolemma nuclei four to five times as numerous as normal. Increase of fat and connective tissue. Vessel walls show great thickening of the adventitia. Intima not involved.

Skoog.—Aged 6 years. Triceps and quadriceps examined. All fibers small, none hypertrophied. Fibers hyaline in appearance. Transverse striations absent in most fibers. Sarcolemma nuclei somewhat increased. Fat and connective tissue increased. Some "arterial capillaries" have thickened walls. Arteries normal.

Biopsy on the 4-year-old brother of this patient showed the same changes.

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† Cases possibly, but not probably, amyotonia; not used in compilation.

THE EPIDEMIOLOGY OF BACILLARY DYSENTERY *

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Bacillary dysentery takes a heavy toll of the infants of large cities every summer. The disease is not spectacular, for it usually does not spread over large areas, but strikes at random here and there and passes by almost unnoticed. During a period of ten years, however, the case incidence is probably higher than the greatly feared poliomyelitis, and the death rate is equally high.

The cause of the disease is well recognized, and its treatment has received careful study, but the mode of transmission has excited only indifference, or, at most, random speculation. Epidemics of adult dysentery have received much attention, particularly during the present war, for the disease has at times wrought havoc among the soldiers. The source and the mode of transmission of the casual case, the sporadic case, the usual type of summer bacillary dysentery of infants is unknown. Kendall[1] believes that the disease in infants is spread by the factors which cause other intestinal infections and emphasizes the importance of contact with carriers. Zinsser[2] has described a small milk epidemic in children, and Amoss and Lucas[3] have established the menace of fly transmission. The Floating Hospital has felt that the most important step in preventing the constant stream of cases of bacillary dysentery that flows to its wards every summer was to undertake the study of the mode of transmission of the disease and the source of infection of the infants.

There are several inherent factors which were most favorable to such a study. The victims were infants, usually under 18 months of age, and therefore their activities were limited; they travel but little, come in contact with few people, and eat only one, or at most but a few articles of food. In fact, we soon found that it was comparatively easy to trace the infection of a baby under 1 year, though much more difficult after the child was old enough to walk, for then they run up and down the street, come in contact with other children, and eat whatever they pick up.

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[1] Kendall: Boston Med. and Surg. Jour., 1913, **69**, 741.

[2] Zinsser: Proc. New York Path. Soc., 1907, p. 162.

[3] Lucas and Amos: Jour. Exper. Med., 1911, **13**, 486.

Another advantage of the study was that the diagnosis of bacillary dysentery is clear cut; with, first, a definite clinical story; second, by means of the isolation of the dysentery bacillus from the stools, and third, the development of specific agglutinin in the blood. It is true that the clinical picture is not always definite, the isolation of the bacillus from the stools is difficult, and the agglutinins develop slowly — in ten to twelve days — and in the mild cases may not appear at all.[4] In this study, no case is reported as positive without showing at least two of the three positive factors.

There are certain well-established facts about the disease which furnish a good working basis.

1. The disease is due to the dysentery bacillus, which has been well described and is readily recognizable.

2. The dysentery bacillus is found in the feces only and not in the other excretions, as in typhoid fever. Thus every case must represent some short path between the infected feces and the mouth of the victim.

3. The incubation period of bacillary dysentery, in adult cases, at least, is short — from three to seven days.

4. The disease in infants is in most instances a summer disease, with highest incidence in July, August, and September.

5. Bacillary dysentery is more common in children of poor parents.

There are certain assumptions that have been believed to play an important part in summer bacillary dysentery of infants.

1. The case incidence of bacillary dysentery bears a close relation to high temperature and high relative humidity.

2. Bacillary dysentery is most common in dirty, unhygienic homes, flourishing among the tenements.

3. Bacillary dysentery is particularly prevalent among the infants of foreigners.

With these facts and assumptions, we had a foundation on which we began to build, adding a few stones to the structure, and tearing down here and there a loose fragment. The investigation included: First, a study of the community conditions and factors affecting every individual. A daily record was kept of the maximum, minimum, and mean temperatures, and of the relative humidity and barometric pressure throughout the summer, in order to show the relation between these factors and the case incidence of bacillary dysentery. Second, beside community conditions, a record of neighborhood conditions was kept. A daily report was received from the boards of health of the city of Boston and all of the neighboring cities, and from the State Board of Health, of all reported cases of bacillary dysentery, in order

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[4] Villard and Dopter: Ann. de l'Inst. Pasteur, 1903, **17,** 463.

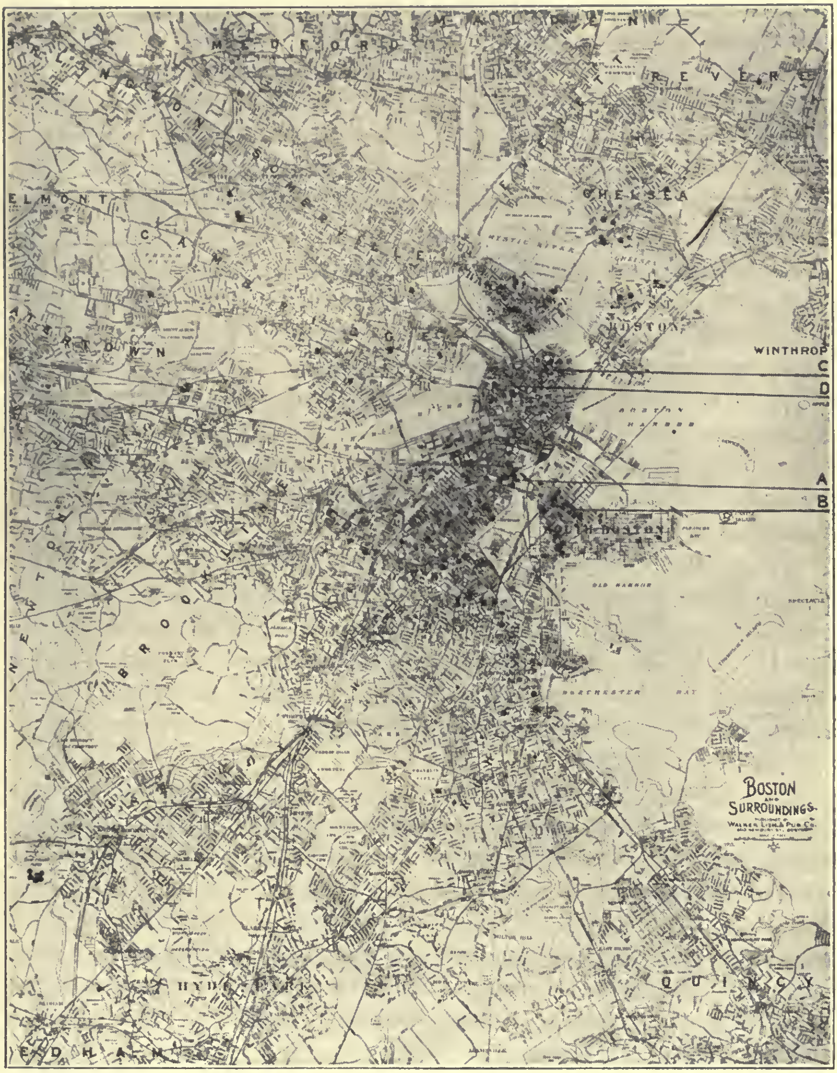

Chart 1.—Spot map of bacillary dysentery of infants in Boston and vicinity during the summers of 1915 and 1916. Each black dot represents a case of dysentery. The nests of infection in certain portions of the South End, A, and in South Boston, B, are striking. Sanitary conditions are equally bad in the North End, C, and West End, D, but the former neighborhoods are occupied largely by first generation Irish-Americans, and the latter by foreigners—Italians, Poles, and Russian Jews. Most factors affecting the health of infants in both neighborhoods are the same, the same water, the same milk supply, the same temperature and humidity, and equal number of flies, etc. The only factor that is not common to both neighborhoods is food, for most foreign mothers nurse their babies, while many American mothers do not.

to expose nests of infection in various parts of the city and state. A spot map was kept of all cases to show the infection centers. Third, the housing conditions of each case were studied, and a score card system of recording the conditions in each home was devised. The nationality of the parents was recorded. Finally, a careful investigation was made of the activities of each infected baby for a period of ten days before symptoms developed. This investigation included food eaten, contact with individuals, places visited, and the history of any illness in the house or neighborhood.

The investigation was begun in each instance from a definite point, a proved case of bacillary dysentery by means of the isolation of the bacillus from the stools. This meant a delay of three to four days, which, together with the three to four days from the beginning of symptoms until entrance into the hospital, made an interval of a week between the onset of symptoms and the beginning of the epidemiologic work. This delay was a serious handicap to the study, but was compensated for by the great advantage of dealing only with proved cases of the disease.

We are able to report the study of seventy-five cases in all, forty-nine of them being hospital cases, while twenty-six cases were discovered in the course of the investigation. The first case developed June 15. The last case studied developed September 1. There was a continuation of the disease after September 1, but the hospital closed September 15, so no more stool diagnoses could be made, and automatically the work stopped.

It is obvious that seventy-five cases are not a sufficient number from which to draw conclusions as to the effect of temperature and humidity on the case incidence of bacillary dysentery. Grover[5] has reported the statistics of several thousand cases of diarrhea in Greater Boston and believes there is close relation between diarrhea of infants and a high humidity and temperature, but so far as our brief studies go, there seemed to be no relation between high temperature and humidity and dysentery. There was one period of severely hot weather, with a corresponding increase in the number of hospital admissions and of infant deaths in the city, but there was no increase in bacillary dysentery. The case incidence is more closely related to the incidence of flies, for the disease had hardly begun before the hot weather was over, and the cases lasted well into September and long after the humid weather was past, though flies were still in abundance.

The disease was not more common in children of foreigners. The most ignorant and destitute foreigners in Boston are the Poles, though the Italians and Russian Jews in certain quarters are living under almost as unfavorable conditions. One would expect, therefore, a high case incidence among these people, but on the contrary, the families chiefly affected were not the illiterate foreigners, but the careless and neglectful poorer class American families, or more particularly the first generation families. A summary of the parentage in the cases is interesting:

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[5] Grover: Jour. Am. Med. Assn., 1916, **67,** 1562.

American, including Canadian	33	Polish	2
American-Irish, first generation	17	French Canadian	2
American-Italian, first generation	4	Negro	1
Irish	4	Greek	1
Italian	4	Unclassified	4
Jewish	3		
		Total	75

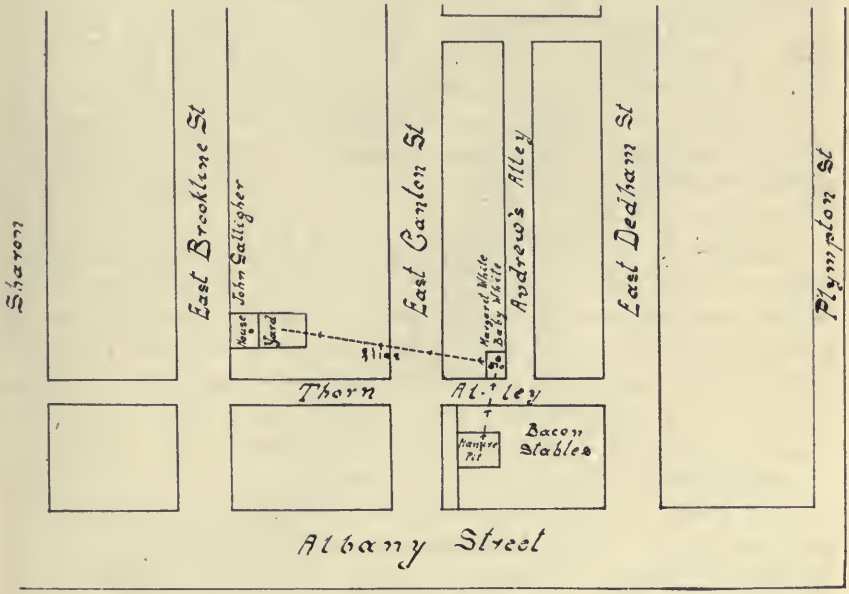

Chart 2.—Diagram illustrating the method of introduction of bacillary dysentery in a community in the early summer, and its mode of transmission. The W. family lived in a miserable unscreened tenement in Thorn Alley. The oldest sister had dysentery in the summer of 1915 and was a carrier. June 26 the younger sister developed dysentery, and since the stools were not disinfected, and flies swarmed into the sick room from a stable across the alley, it is not surprising that the baby brother developed dysentery June 30. J. G., living 150 feet away, also developed dysentery. The two families had nothing in common, but J. G. played in the back yard and was probably infected from the W. family by means of flies.

I do not attribute this surprising situation to the greater uncleanliness or worse sanitary conditions of the American homes, for quite the contrary is the case. It is due to the simple fact that most foreigners nurse their infants, while American mothers often do not. It is interesting to note in this connection that but one of our cases of bacillary dysentery was a nursing baby, and this child was nursed only at night and was fed condensed milk during the day.

Though squalor, poverty, and filth go hand in hand with bacillary dysentery, they are not necessary accompaniments of it, for the disease may be found in the better homes in the better portions of the city and may be entirely absent in the most unsanitary portion of the city. For example, Boston's West End tenement district had almost no cases in the summer of 1916, and the North End very few, though unsanitary conditions are fully as bad in either of these localities as in the South End, where the disease abounded. Young[6] studied the geographic distribution of the Floating Hospital cases in 1910 and found a somewhat similar localization of cases. In 1915 there was a nest of cases in the South End, with twenty or more cases within a radius of only one-eighth of a mile, while in 1916 there were a few scattering cases within this nest, but another nest of cases was found directly across the river in the tenement district of South Boston (Chart 1). Unsanitary conditions, therefore, do not cause dysentery, but they are a fertile soil, needing only the introduction of the seed in order to produce a widespread harvest of cases.

To show the relation between bacillary dysentery and unsanitary household conditions, a housing chart was made of the homes of the infants, based on the score card system, similar to the dairy or market score cards, with a total of 100 points for ideal conditions. Records were kept, for example, of the number of rooms per person, allowing 5 points for a perfect score; of the number of windows per person, 5 points; screening, 5 points; ventilation of living-room, 2 points; of sleeping-room, 3 points; cleanliness and neatness of the house, 5 points; location of the toilet, if clean, well ventilated, and convenient, 5 points; provision for the care of the diapers, if protected from flies, 2 points, if boiled, 3 points. If pasteurized milk was used, 10 points were allowed, and the intelligence of the mother was graded for 10 points.

Forty-one homes were scored, the highest score being 94 per cent., the lowest, 15 per cent., the average 59 per cent. The average housing score in those cases of dysentery due to direct contact, however, was only 48 per cent., and the average housing score of those that were a source of infection to others was 41 per cent. This is but a complicated way of saying that a child is more likely to contract bacillary dysentery if it lives in a dirty, unhygienic house and has a careless and ignorant mother, and a baby with dysentery in a dirty, unhygienic home is most likely to be a source of infection to other children.

The study of the source of infection in the various cases was in the nature of a general survey rather than an intensive investigation.

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[6] Young: Boston Med. and Surg. Jour., 1911, **164,** 299.

The activities of the infected child were studied for ten days before symptoms began, and a careful, detailed record was made of every place the child had been, of all contact with individuals, of all food eaten, or of any factor that might be a source of infection to the child.

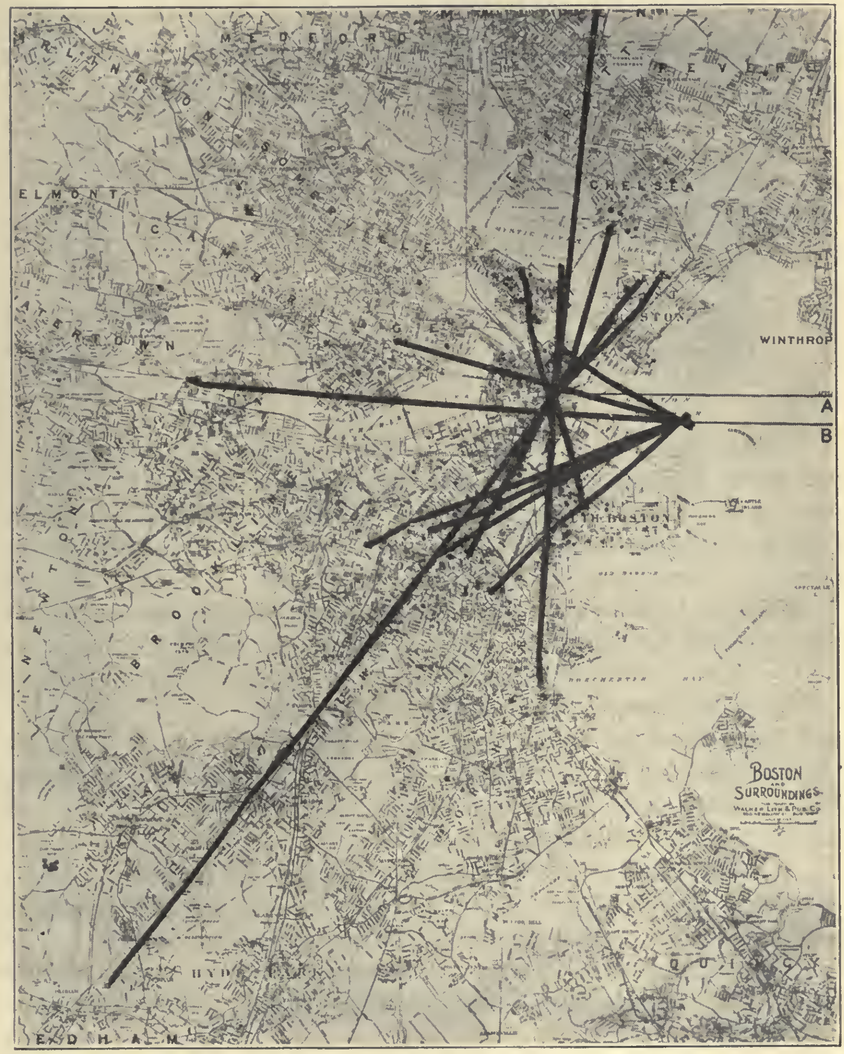


Chart 3.—Map of Boston and vicinity illustrating the epidemiology of widely scattered and isolated cases of bacillary dysentery. Thus, there were fifteen cases in various parts of the city, some of them in isolated suburbs. The only factor in common was S. brand of condensed milk. A. Nine cases were due to the use of icecream cones. B. Twenty-seven cases were due to direct contact. Thus, though we studied seventy-five cases, the foci of infection of these cases were reduced to twenty-eight, and no doubt more intensive study of the cases from unknown sources would have reduced the number of separate foci of infection still more.

A summary of the probable source of infection of the cases is as follows:

Total cases	75
House cases	49
Discovered cases	26, of which 18 were children 8 adults
Average age of hospital case	1 to 2 years
Average age of discovered case	4 to 8 years (other than adults)

Etiology of the seventy-five cases is divided as follows:

	Cases
Contact with an acute case	21
Contact with a carrier	2
Contact with house cases	4
Condensed milk epidemic	15
Icecream "cones"	9
Flies	6
Milk	1
Water	1
Fruit	1
Unknown	15
Total	75

Contact with an Acute Case.—There were twenty-one cases in which the patients developed bacillary dysentery from direct contact with an acute case. These patients were usually of the same family or household and developed the disease during the time the child was at home, or shortly after it was sent to the hospital. Only two of these were hospital admissions, while the remainder were discovered in the course of the investigation. Most of the cases were in older children in the family, though eight of the cases were in adults. In most instances the disease was so mild as to be called "summer diarrhea," and the patients would seldom have seen a physician were it not for the hospital visitor. As a general rule, the older the child, the milder the infection, while only two of the adults were seriously ill, and none of the twenty-one contact patients died.

A typical contact infection was illustrated by the H. family. G. H., 3 years of age, developed bloody diarrhea June 15 and was prostrated and quite ill for several days. The source of her infection was probably an icecream cone. There was no physician in attendance, and the child received poor care. The housing conditions were very poor, scoring only 49 per cent.; a dirty, careless mother, and a dirty, slovenly house. June 19, the mother developed severe abdominal cramps and diarrhea. She took "patent" medicine and was never confined to her bed, though she had "some fever." June 21, Lillian, a daughter 12 years of age, developed diarrhea, but no blood was noted in her stools. She had no physician and was in bed only one or two days. Finally, June 29, Francis, the baby, 8 months of age, developed a severe bloody diarrhea and was brought to the Floating Hospital. The dysentery bacillus of the Flexner type was isolated from his stools and our investigation begun. The blood from the other three members of the family agglutinated the bacillus isolated from the baby's stool in dilutions up to 1 to 300, and also agglutinated other strains of the Flexner type in lesser dilution — up to 1 to 160.

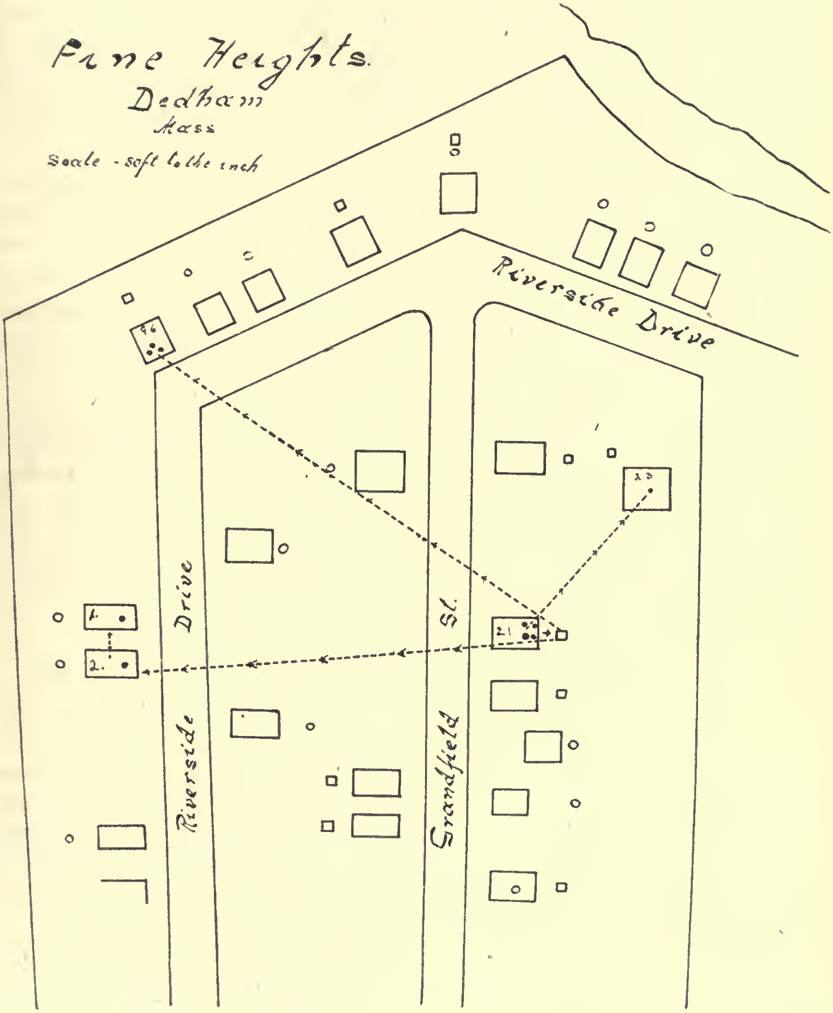


Chart 4.—Diagram illustrating the mode of transmission of the Shiga infection in Pine Heights. L. C. returned from the Haverhill Fresh Air Farm with severe bacillary dysentery and remained in the community three days (House 21). By direct contact she infected two sisters and a brother. A voluntary nurse carried the infection home to her husband (House 23). The infected feces were thrown into an open privy, and flies carried the infection to House 86 and House 2. Raymond G. in House 1 was infected by direct contact from House 2, and from the case of R. G. the investigation began.

Other examples of contact infection with an acute case might be given, but the one instance illustrates the points, and other examples will be mentioned in subsequent paragraphs. The important facts are that many of these contact cases were in older members of the family, and in these persons the course of the disease was mild, so mild that it was commonly called a simple "summer diarrhea." Undoubtedly many cases of summer "ptomain poisoning" are really mild bacillary dysentery. These sporadic cases are seldom serious in themselves, but the patients may be a great menace to the community, particularly to the babies of the community, for our studies have shown that mild adult cases may readily infect a baby, with rapidly fatal results.

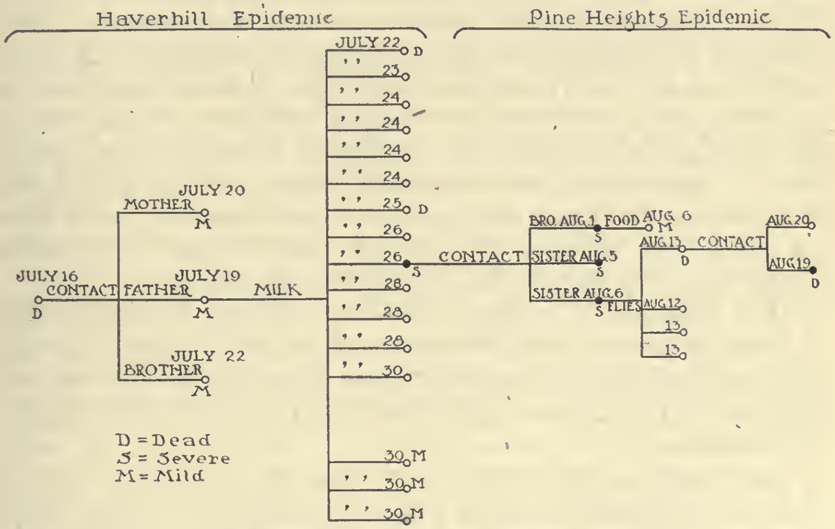
It may be stated as a general rule that in every dirty, careless household visited, where the sick child remained more than one week, there resulted a contact case of bacillary dysentery. There were twenty-one contact cases, from forty-nine house cases, all proved by the isolation of the dysentery bacillus from the stools or by the development of specific agglutinins in their blood. There were other suspected cases, but agglutinins develop slowly, seldom appearing before ten to twelve days, and in mild cases they may not develop at all. No case is reported in which the agglutinins were not present in dilutions of at least 1 to 160. Whenever possible, the strain was used for agglutination which had been isolated from the stool of the corresponding case. In this manner, a greater number of contact cases were proved than would have been possible with the use of a stock strain for agglutinations. As a rule, the blood of the milder cases agglutinated the stock strains, but in lesser dilution than the corresponding strain.

Contact with a Carrier.—In all probability, bacillary dysentery is introduced into the community in the summer by a carrier, and once begun, other factors carry it on. We know there are carriers, but the isolation of the dysentery bacillus from the stool of a carrier is a very difficult thing. I have only two cases to report which seem to be due to contact with a carrier, both cases occurring early in the summer. The W. family is a good illustration of the introduction of bacillary dysentery into a community in the early summer.

M. W., 5 years of age, developed bloody diarrhea June 26 and was brought to the hospital July 2. The Hiss Y-type of dysentery bacillus was isolated from her stools. An investigation showed no illness in the neighborhood and none in the household. The food was not suspected. Her older sister, 15 years of age, had had a severe diarrhea ten months before, lasting about ten days but had no medical attention. We made repeated examinations of this older child's stool but failed to find the dysentery bacillus, though her blood readily agglutinated the strain of dysentery bacilli isolated from her sister's stool in dilution of 1 to 100.

The sanitary conditions of this home were very bad, the housing score being only 15 per cent. M.'s stools were not disposed of for hours at a time and were exposed to flies which swarmed in from a nearby stable.

June 30, Baby W., 3 months of age, developed a moderate, greenish, slimy diarrhea, without blood. Nevertheless, he was sent to the Floating Hospital, and dysentery bacilli were isolated from his stools. July 5, the report came from the city board of health of a case of bacillary dysentery within 150 feet of the W. family, and investigation proved the case to be of the same type as the W. infection. This child, 2 years of age, lived in a clean, sanitary home, under ideal conditions, with a housing score of 86 per cent. He had not been away from home or in contact with other children, and all his food was well cooked. The child commonly played in the back yard, on the side toward the W. family tenement. Since flies were so prevalent in the W. household, since they had ready access to infected diapers, since there were no other cases of bacillary dysentery in that part of the city, the only connecting link between the cases would seem to be the flies (Chart 2).



Shiga Epidemic of Dysentery 1916
Illustrating different modes of transmission in one epidemic

Chart 5.—Diagram illustrating the various modes of transmission of bacillary dysentery in several communities during a single summer. The first infection was from icecream in Lawrence and was transmitted by direct contact to a dairy worker in Haverhill. The dairy worker infected the milk, which infected a large number of children in a fresh air home. One of these children returned to her home in Pine Heights and spread the infection by contact, by flies, and an intermediary carrier.

Another possible contact with a carrier case was R. S., 10 months of age, whose illness began June 30. There were no other cases in that part of the city, the child had not been away from home, and his only food was milk, which was pasteurized. Just one year previously, his sister had been a patient in the Floating Hospital with bacillary dysentery. The same type of bacillus had been isolated from her stools as was obtained from the baby brother's stool. At the time of the investigation, the older child was in perfect health, and repeated examinations of her stools were made for dysentery bacilli, with negative results. The father gave a history of bacillary dysentery during the Spanish-American war. Examination of his stools was also negative, and neither the father's nor sister's blood agglutinated the strain isolated from the baby's stool. Despite these negative findings, it seems probable that either the sister or father was a carrier and infected the baby. This conclusion is open to question because of the difficulty of detecting dysentery carriers. The rest of the story is almost exactly that of the W. infection. After a proper incubation period, the city board of health reported three cases of bacillary dysentery within 100 yards of the L. tenement. In this family, the mother and 3-year-old sister were infected by direct contact with a baby brother. This baby was probably infected from the L. baby by means of fly transmission. These conclusions were reached because flies were abundant and had ready access to the infected stools, there were no other cases of dysentery in the neighborhood, the child had not been away from home, its food was thoroughly cooked, and other sources of infection were excluded.

Hospital Contacts.—Four babies developed bacillary dysentery in the wards of the hospital. Each child was admitted with quite a different diagnosis, and their stools were negative on entrance. Each developed the disease seven to ten days after admission, and in no instance did the child come from an infected home or neighborhood.

This is not a criticism of the hospital staff, but I simply mention these four cases to illustrate the remarkably contagious nature of the disease. In the homes, twenty-one cases were spread by contact with an acute case, and as a rule the infected baby remained in the home less than a week, while but four contact cases developed on the wards, though there were virulent cases on the boat all summer.

It is important to emphasize that extraordinary precautions must be taken to prevent ward infection, and no hospital has a right to admit cases of bacillary dysentery unless it has the facilities for their isolation, for rigid "enteric precautions," and particularly for absolute fly exclusion.

The Condensed Milk Epidemic.—About July 15, patients began to come to the hospital who gave a history of using one of the cheaper brands of a large producer's condensed milk. By August 15 there were fifteen cases from all parts of the city with a clear-cut history of using the S. brand of condensed milk. The epidemic ceased as abruptly as it began.

Case 1.—A baby, 8 months of age, became ill July 8. The child had been fed on S. brand condensed milk for three months. July 5 the mother bought a fresh can, and three days later the child became very ill and was brought to the hospital, where a diagnosis of bacillary dysentery was made. The child had eaten nothing but S. brand condensed milk and boiled water, had not been away from home, and there was no sickness in the neighborhood. A sample from this can was obtained July 13, but no dysentery bacilli were found.

Case 2.—Baby 5 months old developed bacillary dysentery July 14, came to the hospital July 26, and died soon after. The baby had eaten nothing but S. brand condensed milk for three months, had not been away from home, and there were no cases in the neighborhood. Other members of the family, mother, father, and two children, aged 9 and 7, used the same milk, but only in tea or coffee. One child, 2 years of age, used the condensed milk diluted with water. The 2-year-old child developed bacillary dysentery July 24, whether from the milk or from contact with the baby is not known. The father developed bacillary dysentery July 27, the disease running a mild course.

CASE 3.—Baby boy 7 months old, became ill July 17 and was brought to the hospital, where the diagnosis was made. The family lived in an isolated suburb, and the baby was not in contact with other children. The mother was a trained nurse and was intelligent and very cleanly. She carefully boiled the baby's water, then cooled it and added S. brand condensed milk. This was the only food the child had.

CASES 5, 6, 7, 8, 9.—The F. family consisted of mother, father, and four children, aged 4, 3, and 2 years, and the baby of 10 months. The father was a fisherman and was out at sea. August 2, the baby was brought to the hospital with severe bacillary dysentery. The child had been fed on nothing but S. brand condensed milk and boiled water for three months. The mother obtained a fresh can July 24. July 26, the mother and all four children developed a prostrating diarrhea. All recovered in two to five days except the baby. The only food used in common by all was S. brand condensed milk. The only food the baby had had was condensed milk, but the older children had been given bread, butter, eggs, and cooked vegetables, though they had had no icecream, fruit, nor fresh milk. There was but one case of sickness in the neighborhood, a child of 2 years, reported by the city Board of Health as bacillary dysentery. This child's mother had bought a can of the same milk from the same store at about the same time as the F.'s did, and her baby became ill July 23. The parents were noncommunicative and would not permit taking blood for agglutinins, though the history was typical.

Blood was obtained from all the F.'s, however, and all agglutinated the strain isolated from their baby's stool in dilutions of 1 to 160 or higher.

CASE 10.—Mary R., a baby 6 months old, became ill August 3. The mother customarily heated the water to boiling and then added S. brand condensed milk. During the week of July 27 the mother went to work, leaving the baby with a 12-year-old sister. The amateur nurse mixed the S. brand condensed milk with cold water and gave the mixture to the baby without warming it at all. One week after the baby became ill, a 2-year-old sister developed bacillary dysentery, but no physician was called. When seen by the hospital visitor, the 2-year-old child was well, but her blood showed agglutinins in a dilution of 1 to 160 for the strain isolated from her baby sister's stool. This child may have been infected by contact with her baby sister or from the condensed milk. One week later, a cousin 7 years of age developed a moderately severe diarrhea. He had playd with his cousin during her convalescence and was probably a contact case. His blood also showed agglutinins in dilution of 1 to 160.

CASE 11.—Another mother reported that she had not used S. brand condensed milk in the child's food for a month, having substituted a pasteurized milk formula. Later she admitted that the new mixture had not been sweet enough to suit the baby's palate, and though she carefully sterilized the food, she afterward added one-half teaspoonful of S. brand condensed milk to each feeding.

CASE 12.—In one instance, a child of 18 months lived in a suburb under excellent home conditions and was given only pateurized milk. On two mornings, however, the milk delivery was late, and the mother gave the baby a feeding of S. brand of condensed milk. Four days later the baby developed bacillary dysentery.

The finding of dysentery bacilli in the milk is the only evidence lacking to prove that the epidemic was due to S. brand of condensed milk, and without this evidence my case collapses. Stock samples of milk were repeatedly examined, with negative results, and in two instances I was able to obtain the can from which the infection was supposed to have come seven to ten days before. Both samples failed to show dysentery bacilli.

Nevertheless, the evidence is very suggestive. Fifteen cases of dysentery of the same type, from all parts of the city, some of them in isolated communities, developed about the same time, and with but one factor in common, the use of S. brand condensed milk, and in most instances it was the only food of the infected child. None of the hospital admissions for dysentery before July 10 or after August 15 used this brand of condensed milk.

For these reasons, it seems most probable that one portion of one shipment of one brand of condensed milk, delivered about July 10, was infected with dysentery bacilli.

Flies.—Indirectly, flies have already been mentioned as a means of spreading bacillary dysentery. It is a difficult thing to prove anything on a fly. Alice Hamilton[7] found typhoid bacilli on the bodies of flies caught outside a typhoid patient's windows, and Amoss and Lucas[3] caught flies "red-handed" with dysentery bacilli on their bodies.

I believe that seven of our cases are due to infection through the medium of flies, but the evidence is circumstantial only. Several instances of fly transmission have been mentioned in connection with other outbreaks. A typical example of fly transmission may be given.

T. C., 9 months of age, came to the Floating Hospital, August 17, with severe bacillary dysentery. The source of his infection was never discovered. He was taken home against advice August 25, though he was very ill, passing fifteen to twenty bloody stools a day. Ten days later, a baby 3 months old, living just around the corner, developed bacillary dysentery, came to the Floating Hospital, and died. The strain isolated from the stools of both babies were the same type. The two families did not know each other and had nothing in common. The second baby had not been away from home and had been given only pasteurized milk. The back doors of the two families were less than 50 feet apart, and the diapers of the first child were kept on the roof or in an open room for hours without cleansing or disinfection. Flies were in abundance, and neither house was screened. There is no direct proof that flies did carry the infection across that 50 feet from one house to another, but the circumstantial evidence is strongly against the fly.

The other six cases that I have classified as due to fly transmission are almost a repetition of this story. The tenement mother is too ignorant, or many times too careless to protect her baby's stools from flies, and the diapers are seldom boiled. Since flies are so abundant in the tenements, and screens are almost never seen, it is most extraordinary that more cases are not carried in this way. It is more than probable that some of the fifteen cases from unknown sources are due to flies, but as we said at first, it is hard to indict a fly.

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[7] Hamilton: Jour. Am. Med. Assn., 1903, **40**, 576.

Icecream.—It is a curious thing that a city which is so careful about its milk supply and other foods should practically neglect a food that is almost as universally consumed, in the summer, at least, as milk itself. Icecream "cones" are the presumable source of infection in nine of our cases. The evidence is not absolute, for most of the children were older than in the other types of infection — between nine months and four years — and their activities were more varied. They played in the streets, ate various articles of food, and came in contact with many children, and thus their epidemiology is much more indefinite than that of infants.

In each case attributed to icecream, the infection came through the one cent icecream "horn" sold in the filthy basement confectionery shops. In each instance, the criteria were that the child had not been away from home, had not been in contact with sick children, there were no other cases of dysentery in the neighborhood, other food eaten was beyond suspicion, and the icecream was eaten within six days.

A good example is the Jack Frost Ice Cream Company's cones.

R. K., 15 months old, lived in a splendid home in a suburb. There were no cases of dysentery for miles, and the child had not been away from home. July 30 she was given an icecream "horn" of the Jack Frost Company, and August 3 developed bacillary dysentery and was brought to the Floating Hospital.

J. W., 4 years of age, lived in another part of the city in a sanitary home and under intelligent care, and there were no cases of bacillary dysentery in the neighborhood. The child ate a Jack Frost icecream cone July 22. Symptoms developed July 24, and he was taken to the Children's Hospital, where he died. Dysentery bacilli were isolated from the stools of both children and were of the same type.

August 3, a sample of icecream was obtained from the Jack Frost Icecream Company. There were seven million bacteria per cubic centimenter, with colon bacilli in 1/1,000 of a cubic centimeter. Dysentery bacilli of the Flexner type were actually isolated from the sample of icecream. This is the only instance in which we were able to isolate dysentery bacilli from icecream cones, though total bacterial counts and colon bacilli counts always showed very undesirable conditions.

Water.—The one outbreak that could probably be attributed to water was a short but severe one.

W. M., 3 years old, lived in a large suburban home in a newly constructed portion of the city, with ideal conditions for outdoor exercise. The child had not been away from home, and had played with no children except his older sisters. The building of new streets had opened up a spring which filled a pool in the roadside in front of the house, and from this the workmen used to drink, and sometimes also washed their hands in it. One day the child followed their example. There had been clogging of the nearby house sewers eight to ten days before, and the sewage had been pumped from the cellar into the street about 100 feet above the spring. Aug. 4, four days after the child drank from the spring, symptoms of dystentery developed, and he died in three days. The child was nursed by his father and mother, and the older children frequently came to his bedroom. August 7 the mother and a 6-year-old sister developed dysentery, and the father became ill August 8. All were severely infected, but eventually recovered. The blood from both father and mother developed agglutinins for the Hiss Y-type of dysentery bacillus in dilutions of 1 to 320. This same type was isolated from the father's stool. A careful study was made of the food eaten by the family, and all other possible sources of infection, and the conclusions reached were that the three secondary cases were probably contacts from the baby, and that the baby was infected from drinking the water in the spring. This water was analyzed bacteriologically, August 24. Total bacterial count, 2,700 per c.c. Coli in 1/100 of a cubic centimeter. Careful search was made for dysentery bacilli, but none were found.

The Shiga Epidemic.—There was one epidemic of dysentery due to the Shiga bacillus which threaded a devious and devastating path through several communities and gave us the best single example of the various modes of transmission of bacillary dysentery.

Baby H. P., 2 years of age, was taken to Lawrence, Mass., July 14, where he was given some icecream. The child developed acute enteritis, July 16, was taken to the Gale Hospital July 19, and died. The father developed diarrhea July 19, the mother July 20, and another child July 22. All were moderately ill, and the father continued to work throughout his illness. Mr. H. P., Sr., was a milker in the R. dairy, which sent almost its entire milk supply to a Fresh Air Home for children in Haverhill. There were about seventy-five children in this summer camp, from 7 to 14 years of age, most of them coming from Boston and vicinity. July 24 the first case of bacillary dysentery developed in the home, and within four days there were twenty more cases, all quite ill. The superintendent at once closed the Fresh Air Home and sent all the children to their homes.

One of the children, L. R., 9 years of age, was sent to her home in Pine Heights, an unsanitary Boston suburb. She was very ill and remained at home only three days, after which she was taken to the Children's Hospital. She remained at home long enough, however, to infect her two sisters, aged 5 and 7 years, and her brother, aged 11 years, who developed symptoms August 3, August 5 and August 6. August 8 all of them were taken to hospitals, the two younger being quite ill. A neighbor had helped in the care of these children, then returned to her home and prepared her husband's supper. August 9 he developed a moderately severe dysentery.

The dejecta from the C. children was thrown down the pit of an open privy without disinfection. August 12, a neighbor's child, L. E., 2 years old, living directly across the street from the C.'s, developed bloody dysentery and died in three days. This family had not come in contact with the C. family, but since flies were so prevalent, both in the E. kitchen and in the C. privy, I believe the infection was carried across the street by flies.

August 12 and 13 three adult neighbors in one family all developed severe diarrhea, which persisted for a few days only. These cases had not been in contact with the C. family and are possible fly infections.

August 20 the baby brother of L. E. developed a moderate diarrhea, but dysentery bacilli were never recovered from his stools. August 21 R. G., a 2-year-old child living next door to L. E.'s, developed bacillary dysentery. He had been playing with L. E. the week before and probably was a contact case. This child was brought to the Floating Hospital, August 25, and died that night. Shiga dysentery bacilli were isolated from his intestinal wall, and from this case our epidemiologic investigation of the Shiga epidemic began, gradually developing the various details that have been described (Charts 4 and 5).

CONCLUSIONS

1. Bacillary dysentery is a readily communicable disease which may be spread in a community by means of contact with an acute case or a carrier, by means of food, as milk, condensed milk and icecream, by water, and by flies.

2. The sporadic summer bacillary dysentery of infants may be transmitted to older children or to adults. Though the disease is severe in the infant, it is usually mild in older children or adults. As a general rule, the older the child, the milder the disease.

3. The dysentery bacilli from the stool of an adult with a mild case of dysentery may produce a rapidly fatal dysentery in infants. Thus the menace of the mild adult case to the community is considerable.

4. Bacillary dysentery is rarely found in a nursing baby.

5. Hospital contact cases are not uncommon. The disease is very readily transmissible by direct contact, and no hospital has a right to admit patients with dysentery unless it can make provision for their isolation.

HYPERTENSION IN NEPHRITIS IN CHILDHOOD, WITH A STUDY OF NINETY-THREE CASES *

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A recent and unusual case of high blood pressure in nephritis in a boy of 10 stimulated a review of the literature to ascertain the frequency with which, and to what degree, hypertension occurred in nephritis in children. Considering the attention blood pressure has received in the nephritis of adults, we were immediately struck by the scarcity of literature relating to blood pressure in nephritis occurring in the early years of life.

Shaw[1] reports three cases of acute nephritis in children with blood pressure readings, and concludes that "hypertension in acute nephritis, so constant in adults, is not so marked in children." Gordon[2] reports the blood pressure in nine cases, seven of which were acute nephritis and two chronic cases with acute symptoms superimposed. He found that the blood pressure in acute nephritis is elevated, and that the increase may be very great, one of his cases having a pressure of 180 mm. Hg. He also pointed out that the cases with the highest pressure show very little edema, but have large amounts of blood in the urine. The large amount of blood, he believes, is due to a rupture of renal capillaries by increased pressure. Barber[3] reports three cases of chronic interstitial nephritis in children. The blood pressure was below 100 mm. Hg on several occasions in the one case that he tested. Wessler[4] found a latent hypertrophy of the heart occurring in nephritis in children which he believes is secondary to arterial hypertension. Bugge[5] asserts that the blood pressure in both orthostatic and nephritic albuminuria is usually normal. Bass and Wessler,[6] after analyzing twenty-six cases of orthostatic albuminuria, conclude that the blood pressure differs but little from normal. Thus, while increased tension is expected, according to most authors, the evidence is not conclusive, and no figures have been reported giving the constancy or extreme limits of the increase.

In the records of the Massachusetts General Hospital and the medical service of the Children's Hospital, ninety-three cases of nephritis

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* Submitted for publication Dec. 26, 1916.

* From the Children's Medical Department, Massachusetts General Hospital, and the Medical Service of the Children's Hospital, Boston.

1. Shaw, H. L. K.: Albany Med. Ann., 1900, **21,** 88.
2. Gordon, Lennox: Arch. Pediat., 1911, **28,** 343.
3. Barber, Hugh: Brit. Med. Jour., Nov. 8, 1913, p. 1204.
4. Wessler, H.: Arch. Int. Med., 1914, **14,** 517.
5. Bugge, J.: Norsk Mag. f. Laegevidensk., 1913, **74,** 1601.
6. Bass and Wessler: Arch. Int. Med., 1914, **13,** 39.

in children between the ages of 2 and 12 years were found in which blood pressures had been recorded. Sixty-five of these cases were diagnosed as acute nephritis and twenty-eight as some form of chronic nephritis. No attempt has been made to subdivide the cases of chronic nephritis into the different pathologic classes. These cases have been taken as the basis of this report. They cover a period of several years and represent the observations of numerous men. Deductions from these records are open to criticism on several points. In no case is the size of the cuff used mentioned, the importance of which has been pointed out by Judson and Nicholson[7] and P. Wolfensohn-Kriss.[8] The personal factor in blood pressure observations has been pointed out by Kilgore[9] and by Kilgore, Berkley, Rowe and Stabler.[10] The importance of the phase taken for the reading has been pointed out by numerous observers. We feel, however, that some value may be attached to these findings, and it is hoped that this report may lead to further investigation along the same line in which all of these factors have been properly controlled.

The blood pressure of normal children has been studied by several observers from different points of view. As early as 1900 Shaw[1] reported 400 observations on forty-five children, using Gartner's tonometer. P. Wolfensohn-Kriss[8] and M. Michael[11] report the relation of the blood pressure to the body weight and the height in normal children. Other investigators who should be mentioned are Cook,[12] Stowell and Gordon,[13] Gordon,[2] Nirrnheim,[14] Oppenheim and Bauchwitz,[15] Kaupe,[16] Mello Leitao,[17] Katsenberger[18] and Rolleston.[19] The most recent and most exhaustive work is that of Judson and Nicholson.[7] These authors give a complete summary of the work up to date and should be consulted by those interested in the subject. They also report a series of 2,300 observations of their own which they have tabulated, the pressures being those of normal children between the ages of 3 and 15 years. Their results are taken as a standard for comparison in this paper, though as stated above, we do not claim such accuracy as theirs.

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[7] Judson, C. F., and Nicholson, P.: Blood Pressure in Normal Children, Am. Jour. Dis. Child., 1914, **8,** 257.

[8] Wolfensohn-Kriss, P.: Arch. f. Kinderh., 1910, **53,** 332.

[9] Kilgore, E. S.: Arch. Int. Med., 1915, **16,** 934.

[10] Kilgore, Berkley, Rowe and Stabler: Arch. Int. Med., 1915, **16,** 927.

[11] Michael, M.: A Study of Blood in Normal Children, Am. Jour. Dis. Child., 1911, **1,** 272.

[12] Cook, H. W.: Am. Jour. Med. Sc., 1903, **125,** 433.

[13] Stowell: Albany Med. Jour., 1900.

[14] Nirrnheim, E.: Kinderheilsanst; Dresden Dissertation, Kiel, 1913. Also Monatschr. f. Kinderh., 1914, **12,** 20.

[15] Oppenheimer and Bauchwitz: Arch. f. Kinderh., 1905, **42,** 415.

[16] Kaupe, W.: Monatschr. f. Kinderh., 1910-1911, **9,** 257.

[17] Leitao, Mello: Arch. de med. d. enfants, February, 1913.

[18] Katsenberger, A.: Ztschr. f. Kinderh., 1913, **9,** 167.

[19] Rolleston, J. D.: Brit. Jour. Dis. Child., 1911, **8,** 433.

For the purpose of comparative study the cases here reported have been grouped as follows:

1. Nephritis in general (including all cases regardless of type).
2. Acute nephritis, sixty-six cases.
3. Chronic nephritis, twenty-seven cases.

Table 1 shows the distribution of these cases as to age, type of nephritis and the number of systolic and diastolic observations for each age.

Clinical notes in all cases but one have purposely been omitted. The following case, however, is given in detail because of certain unusual features.

TABLE 1.—Author's Cases Showing Type of Nephritis and Number of Blood Pressure Observations

Age	Total Number Cases	Number of Acute Cases	Number of Chronic Cases	Number of Systolic Observations	Number of Diastolic Observations	Total Observations
2	3	2	1	3	3	6
3	4	3	1	6	5	11
4	11	10	1	24	15	39
5	9	9	0	16	16	32
6	9	7	2	13	11	24
7	11	7	4	17	8	25
8	10	6	4	34	16	50
9	14	12	2	32	12	44
10	8	1	7	20	6	26
11	10	7	3	25	20	45
12	4	2	2	26	1	27
	93	66	27	216	113	329

REPORT OF CASE

History.—M. F., boy, aged 10 years, entered the Massachusetts General Hospital for diagnosis. The family history was negative, and there was no evidence of specific disease.

Past History.—Full term, normal delivery, normal at birth, and weighed 8 pounds. No coma or convulsions. Breast fed for three weeks and then discontinued because the child had three convulsions (general rigidity with clonic contractions). He was subsequently fed on modified cow's milk and did poorly. He had measles at 6 years, whooping cough at 6½ years, mumps when 7 and chickenpox when 7½ years of age. He had not had scarlet fever, diphtheria, rheumatism, chorea or tonsillitis.

Present Illness.—Complaint, headache and failing vision. The patient was apparently perfectly well up to two months before entry to the hospital, when his mother noticed that he held papers close to his eyes when reading. Six weeks previous to admission to the hospital his teacher reported that his vision was imperfect, but he continued in school three weeks after this and then had glasses fitted by an optician, with no improvement. An oculist consulted shortly after this offered no satisfactory explanation. Since onset of present illness he had had occasional attacks of headache and vomiting. The headaches were always frontal, sometimes radiating to the occiput. They came at no definite time, being present at times when he awoke in the morning and sometimes coming on during the day. Occasionally he had headache after reading. During the week previous to entering the hospital the headaches were unusually severe and were accompanied by vomiting. For two days he had had no pain. The vomiting bore no relation to meals and was definitely propulsive. There was no marked change in disposition, though the mother thought the boy had been more "cranky" recently. He had no staggering, twitchings, convulsions, diplopia, blurring of vision, dyspnea, cyanosis or edema. No nocturia, frequency, bloody or smoky urine had been noted. The mother believed his eyes had been puffy at times, but was not sure.

Physical Examination.—A fairly well developed, thin, sallow, white boy of about 10 years. Pupils equal, regular; react to light and distance. There was a lateral nystagmus and a marked albuminuric retinitis. Tonsils moderately enlarged. Multiple shotty glands palpable in cervical, axillary and inguinal region; epitrochlears palpable. Left border cardiac dulness 9 cm. to left of midsternal line; right border 3.5 cm. to right of midsternal line. Apex impulse diffuse and forcible. Sounds regular, slow and of good quality; no murmurs. Aortic second sound was greater than pulmonic second sound, and loudly accentuated. At aortic area there was a gallop rhythm. Palpable and visible impulse in second interspace, 3.5 cm. to right of midsternal line. Palpable pulsation in suprasternal notch. Pulses equal, synchronous and of high tension. Arterial wall distinctly palpable after pulse had been shut off by compression. Lungs normal. Abdomen normal, liver and spleen not palpable. Extremities normal, no edema. Knee jerks equal and exaggerated. Achilles reflexes active, with suggestion of clonus on the right. Physical examination otherwise normal. The blood pressures in this case on entry were, systolic 250 mm. Hg, and diastolic 210 mm. Subsequent readings were

Systolic	250	218	210	210
Diastolic	190	190	180	180

Clinical Notes.—On a dry diet (360 c.c. fluid intake) 1,560 c.c. of urine were excreted with a specific gravity of 1.005, which indicated an inability of the kidneys to excrete salts in a concentrated form.

The carbon dioxid tension of the alveolar air was 42.8. The urine became neutral in reaction after the administration of 1 gm. of sodium bicarbonate by mouth. Both of these tests showed the absence of acidosis.

After the administration of 10 gm. of urea by mouth the urine for the following twenty-four hours contained but 5.3 gm. (urease method), indicating a marked decrease in the ability of the kidneys to excrete nitrogen.

Nonprotein blood nitrogen, 40 mg. per 100 c.c. of blood.

Urine: Sp. Gr. 1.005; albumin, heavy trace; sugar, 0; acetone, 0; sediment showed many hyaline and granular casts; no blood cells.

M. F. was discharged unrelieved with a diagnosis of chronic nephritis and an unfavorable prognosis given to the parents. Death occurred at home three weeks after leaving the Massachusetts General Hospital. Unfortunately no postmortem examination was made.

This case shows that the blood pressure in nephritis in childhood may be tremendously increased, even reaching a point usually seen only in well marked adult cases. Hypertension of this degree is unusual in children, and in our series only seven cases show a pressure of 150 mm.

Hg or above, four of these being acute and three chronic nephritis. Only five additional cases had pressures as high as 140 mm. Hg, three acute and two chronic cases.

Headache, so prominent a feature in this case, is an uncommon symptom. It is mentioned in but one other case in the entire series, a child, aged 10 years, with chronic nephritis, uremia, temporary blindness, and having a blood pressure of 170 mm. Hg.

Changes in the fundus secondary to nephritis apparently are very uncommon in childhood. We have found no mention of such changes in the literature, and such changes were found in but one other case in the series, a boy, aged 10 years, with a systolic pressure of 210 mm. Hg, who died two weeks after leaving the hospital. These two cases are the only ones in the entire series of ninety-three cases having systolic pressures of over 200 mm. Hg. In the case recorded there was a well marked albuminuric retinitis, with large patches of exudate and numerous small hemorrhages in each eye. Whether these changes are frequently present and are not looked for, or are extremely rare, it is of course impossible to say. It seems probable, however, that the condition but rarely occurs. This condition in adults is generally considered a prognostic sign of some importance, and the rapid, fatal outcome in both of these cases suggests that it may carry with it a similar prognosis in children.

It is of interest to note that in this case, with a tremendously increased blood pressure, there were no blood elements found in the urine.

As is not infrequently the case in nephritis in children, no etiology for the nephritis could be found in this case.

COMPARISON OF THE BLOOD PRESSURES OF NEPHRITIC AND NORMAL CHILDREN

Believing that the blood pressure is raised in the nephritis of children, it becomes of interest to know the constancy and extent of this rise. In Figure 1 we have shown the averages of all the blood pressures in the ninety-three cases of nephritis compared graphically with the normal figures of Judson and Nicholson. This figure shows that although there are slight variations, there is a definite increase in both systolic and diastolic blood pressures in nephritis when compared with the normal blood pressure for the corresponding age. In our series this increase averages about 20 mm. Hg for systolic and about 10 mm. for diastolic readings.

The diastolic pressures showing a less marked increase over the normal, indicate that in nephritis in childhood there is an increase in the pulse pressure. The extent of this increase is shown in Table 2, the normal figures being those of Judson and Nicholson. It is readily seen that this increase is not a constant factor and varies between the wide limits of 0.1 and 21. The normal pulse pressure as given by other observers also show wide variations from those given by Judson and Nicholson, and for this reason we feel that further studies are necessary definitely to decide the effects concerning the pulse pressure in nephritis in childhood.

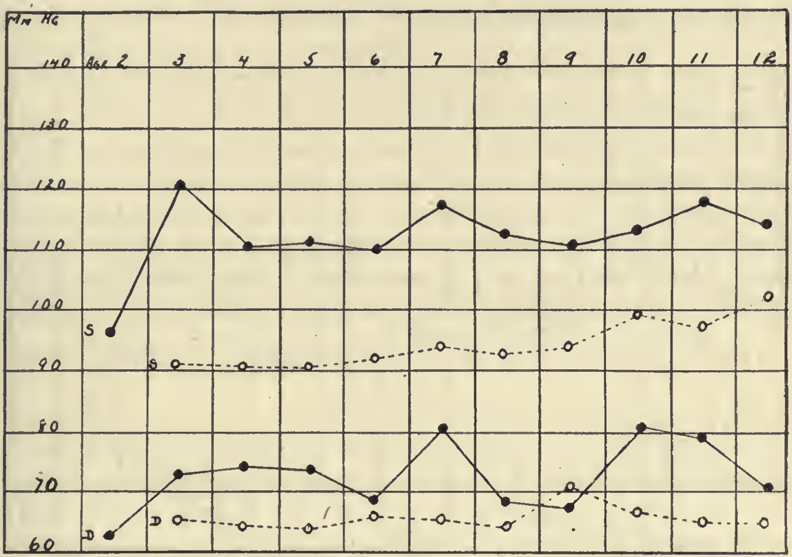

Fig. 1.—Curves showing averages of the blood pressures in ninety-three cases of nephritis compared with the normal figures of Judson and Nicholson. S = systolic; D = diastolic; O—O = normal; •—• = nephritis.

TABLE 2.—Normal Pulse Pressures Compared to Those of Nephritis

Observers	Age, Years										
	2	3	4	5	6	7	8	9	10	11	12
Normal pulse pressure, Judson and Nicholson...	—	26.2	26.7	26.9	25.3	26.9	28.9	23.3	32.1	31.5	37.1
Nephritic pulse pressure, Berkley and Lee..........	34	47.2	35.1	37 0	30.5	36.5	44.0	44.3	32.2	38.4	42.6
Increase over normal......	—	21.0	8.4	10.1	5.2	9.6	15.1	21.0	0.1	6.9	5.5

COMPARISON OF THE BLOOD PRESSURES OF CHRONIC AND ACUTE NEPHRITIS

In order to ascertain whether in children chronic nephritis showed higher blood pressures than acute nephritis, we have in Figure 2 compared the average blood pressures of our patients in these two groups. The differences are not sufficient and are too irregular to warrant drawing definite conclusions. It would seem that there is no increase in the blood pressure of chronic nephritis over that of acute nephritis in childhood. It is possible, however, that in a larger series some difference might be shown. It was found impossible to study the effect of such factors as severity, type of involvement, or duration of the disease in our cases. The highest systolic pressure among our acute cases was 190 mm. Hg (in a child of 4) and among the chronic cases, 250 mm., the case above reported.

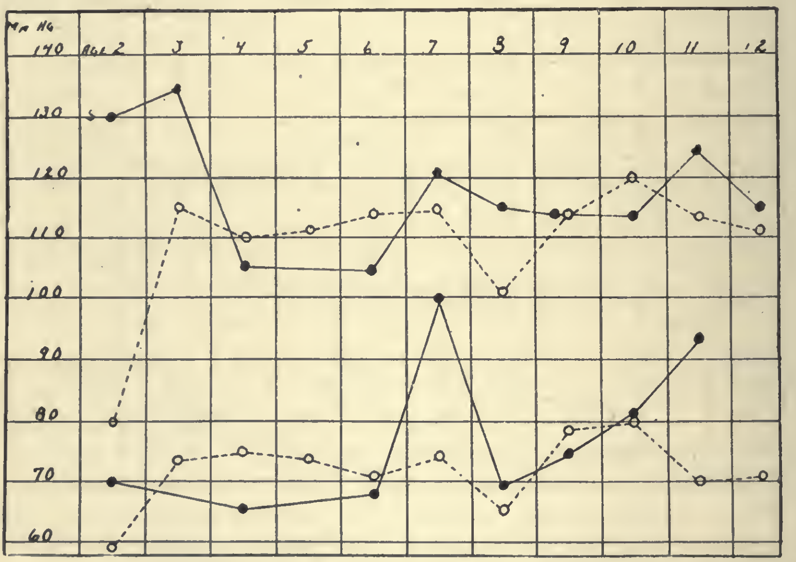

Fig. 2.—Curves comparing the blood pressures of acute nephritis with those of chronic nephritis. S = systolic; D = diastolic; o—o = acute nephritis; ●—● = chronic nephritis.

EDEMA AND BLOOD IN THE URINE WITH RESPECT TO BLOOD PRESSURE

Since Gordon has stated that patients showing the highest blood pressures had comparatively little edema and a large amount of blood in the urine, we reviewed the forty-one cases from records of the Massachusetts General Hospital with these points in view. Thirty-three patients showed a more or less marked edema, while eight showed very little or none. The average blood pressure in those patients having edema was 123.8 mm. Hg. The average systolic blood pressure of those with little or no edema was 112 mm. Hg. Twenty patients with large amounts of blood in the urine had an average systolic blood pressure of 112 mm. Hg, while twenty-one having little or no blood had an average of 126 mm. Hg. In each instance in which the systolic blood pressure has averaged above 150 mm. Hg the urine has been found to show but little blood. The degree of edema in our patients having a systolic pressure of 150 mm. or over has been found to vary from "very slight" to "well marked." These results show that there is probably no definite relation between the increase in the blood pressure and the amount of edema present or the amount of blood in the urine, as suggested by Gordon. The amount of blood we believe is relative to the severity of the pathologic process present rather than to an increase in blood pressure. The amount of edema probably varies with the ability of the kidneys to excrete salts.

URINARY FINDINGS COMPARED WITH BLOOD PRESSURE

We have reviewed the urine charts in these same cases to find, if possible, any relation between the increase in blood pressure and the amount of albumin or number of casts in the urine. Blood pressures were also compared with the specific gravity of the urine. So far as we were able to determine, no relation exists between the blood pressure and any of these factors. That the urinary findings bear no relation to the pathology of kidney lesions has been shown by Stark.[20]

SUMMARY

From a study of blood pressure observations in ninety-three cases of nephritis in children between the ages of 2 and 12 years, we may say that

1. The blood pressure is elevated in the nephritis of childhood, and occasionally to a marked degree. This applies to both acute nephritis and chronic nephritis.
2. Systolic and diastolic pressures are not increased to the same degree, the former averaging about 20 mm. Hg, and the latter about 10 mm. above normal.
3. The pulse pressure is increased, but the factor is not constant.
4. The blood pressure in chronic nephritis shows no constant elevation above that of acute nephritis.
5. The blood pressure may, in rare instances, be of prognostic value.
6. No relation has been found to exist between the blood pressure and the urinary findings.
7. Patients having marked edema showed a slightly higher average blood pressure than those with little or none. This difference is not great enough to warrant definite conclusions.
8. Albuminuric retinitis is probably not common even in cases showing a marked increase in blood pressure.

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[20] Stark, J. R.: Jour. Lab. and Clin. Med., November, 1916, p. 134.

PROGRESS IN PEDIATRICS

REVIEW OF RECENT LITERATURE ON CONDITIONS OF ABNORMAL METABOLISM IN INFANTS *

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ACUTE DISTURBANCES OF NUTRITION

Metabolism Studies in "Dyspepsie" and "Intoxikation."—Jundell[1] has studied the fat, nitrogen and mineral metabolism in two cases of "Dyspepsie" and in two cases of "Alimentären Intoxikation." The four infants were quite young, their ages ranging from 4 to 8 weeks, and all of them developed the conditions investigated while taking buttermilk to which was added a large amount of sugar. The sugar content of the milk was 8 per cent., and in one instance, 10 per cent. The food was continued through the periods during which the metabolism was studied. The symptoms of the condition designated "Dyspepsie" were severe diarrhea, five to ten thin, slimy or watery stools daily, occasional vomiting and stationary or declining weight. The onset of the symptoms was fairly abrupt. Two experimental periods of several days' duration were obtained from each infant. In the case of the infants developing "Intoxikation" there was, with the diarrhea, an abrupt and rapid loss of weight, an initial rise of temperature, and then a deepening of respiration, stupor and the appearance of sugar in the urine. A single twenty-four hour period was obtained from each of the infants, after which they were given water and then protein milk, and in both instances gradually recovered. Although so short a metabolism period is not entirely satisfactory, the author maintains that the disturbances of metabolism in "Intoxikation" progress so rapidly that the figures obtained are acceptable. In reviewing the author's results, normal figures given for comparison are indicated by enclosing them in parentheses. These normal figures are those provided by the author or else they were obtained from Tobler and Bessau.[2] Since so many factors in normal metabolism are variable, such figures possess only an approximately "normal" value. All of the absolute figures given are for per diem quantities.

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[1] Jundell: Ztschr. f. Kinderh., 1913, **8**, 235.

[2] Tobler and Bessau: Allgemeine Pathologische Physiologie der Ernährung und des Stoffwechsels im Kindesalter, Weisbaden, 1914.

The author's results show strikingly the effect of diarrhea in decreasing the volume of urine excreted. In "Dyspepsie" the average urine volume was 117 c.c. and in "Intoxikation" it was 40 c.c. (normal 500 to 600 c.c.). The amount of stool in "Dyspepsie" was 250 gm., in "Intoxikation" it was 312 gm. (normal 20 to 50 gm.). Urine and stools together amounted in "Dyspepsie" to 370 gm. and in "Intoxikation" to 350 gm. (normal 500 to 700 gm.), showing that in diarrhea less water is carried from the body in the stools and urine together than normally. That this is not due to a lack of water intake is shown by figures for urine and stool excretion per 100 c.c. of food. They were, for "Dyspepsie," 54 gm., for "Intoxikation" 60 gm. (normal 64 gm.). If diarrhea is accompanied by a desiccation of the tissues, as is often inferred, this cannot be due to the watery stools per se, and can only be explained by assuming a greater than usual water loss through the skin and lungs. The absorption of nitrogen from the intestine in percentage of nitrogen in the food was, in "Dyspepsie," 78 per cent., as compared with 90 per cent. absorbed by normal infants. The nitrogen retained in percentage of intake was in one instance 28 per cent., in the other 49 per cent. (normal 33 per cent.). The absolute retention was 0.68 gm. and 1.22 gm. (normal 0.8 gm.). By an increased retention the body therefore managed to obtain its nitrogen need in spite of the diarrhea. In the "Intoxikation" cases the absorption of nitrogen was much lower than normal — 58 per cent and 34 per cent. of the intake. In the first instance there was an absolute retention of 0.63 gm., or 32 per cent., of the intake; in the second, the nitrogen balance was negative, showing a loss of 0.34 gm. The absorption of fat was in "Dyspepsie," 57 per cent. of the intake (normal 90 to 98 per cent.). In "Intoxikation" the absorption was 46 per cent. and — in the more severe case — only 12 per cent. The utilization of fat is therefore lower than normal in "Dyspepsie" and very low in severe "Intoxikation." Analysis of the stool fat showed in both "Dyspepsie" and "Intoxikation" about the same partition into neutral fat, fatty acids, and soaps. In average there was found 20 per cent. of the total fat, as neutral fat, 63 per cent. as fatty acids and 17 per cent. as soaps. Reliable normal figures, especially for the fatty acid and soap ratio, have not been established. Nieman found in a normal 3½ months infant practically no neutral fat in the stool, 97 per cent. of the total fat as fatty acids and only 3 per cent. as soaps. The retention of total ash was in average in one case of "Dyspepsie" 20 per cent. of the ash in the food, and in the other 9 per cent. (normal 11 to 23 per cent.). The total mineral balance was negative in both cases of "Intoxikation." As regards the constituents of the ash, the retention of calcium and phosphorus was least affected by the diarrhea, whereas there was marked loss of the alkaline metals, sodium and potassium. Magnesium was not determined. In "Dyspepsie" the retention of CaO was 0.27 gm. and 0.248 gm. (normal 0.13 gm. to 0.23 gm.). In "Intoxikation" it was 0.202 gm. and 0.026 gm. There was thus in spite of the diarrhea a normal CaO retention except in the more severe of the 'Intoxikation" cases. A positive balance for P_2O_5 obtained both in "Dyspepsie" and "Intoxikation," although the amounts retained were possibly somewhat less than normal. The balance for K_2O was positive in both cases of "Dyspepsie," 0.18 gm. and 0.13 gm. being retained (normal 0.18 gm. to 0.32 gm.). In "Intoxikation" there was a negative balance with a loss of 0.15 gm. and 0.35 gm. In one case of "Dyspepsie" the Na_2O balance was positive, 0.051 gm. (normal 0.08 gm.?), in the other it was just negative, — 0.005 gm. It was markedly negative in both cases of "Intoxikation," — 0.27 and — 0.31. The chlorin balance was positive in one case of "Dyspepsie," the amount retained being 0.046. In the other case there was a loss of 0.064 gm. In both cases of "Intoxikation" the balance was negative, — 0.112 and — 0.250. These results are in accord with the finding by Holt, Courtney and Fales[3] that there is in diarrhea a relatively much greater loss in the stool of chlorin and of the alkalies than of calcium and magnesium.

The author regards his results as confirming Finkelstein's definition of "Dyspepsie" as a disturbance entirely local in character, limited sharply to the gastro-intestinal canal and not directly interfering with nutritional processes going on within the body. In contrast there is in "Intoxikation" a general upset of metabolism, with destruction of body tissue, as indicated by a negative nitrogen and mineral balance. He explains the positive nitrogen balance in one of the "Intoxikation" cases as most probably due to an inability of the organism to excrete effete nitrogen. He believes that he has established Finkelstein's view that "Dyspepsie" and "Intoxikation" are unrelated entities by showing that the disturbances in metabolism are in the two conditions distinctly different. It is much easier, however, unless one desires to support Finklestein's preconception, to make just the opposite inference from the author's results, namely, that the disturbances detected in "Dyspepsie" could by progressing simply in degree become those obtaining in the condition designated "Intoxikation."

Relation of Volatile Fatty Acids in the Intestine to Diarrhea.—Bahrt and co-workers have investigated the possibility of a causative relation of the volatile fatty acids in the intestine to diarrhea. Their evidence in this direction is much more nearly quantitative than that which has been presented by other workers. Bahrt and Bamberg[4] by experiments with dogs demonstrated that the lower or volatile members of the fatty acid series are capable of increasing peristalsis when administered in relatively small amounts. The degree of effect produced by the same sized dose of the various volatile fatty acids they found to be roughly inversely proportional to their molecular size. Considerably more butyric or caproic acid had to be given to obtain an increase in peristalsis than of acetic acid, the lowest member of the series present in the intestine. Using the bismuth and Roentgen-ray method of Cannon, they studied the effect on stomach and intestinal peristalsis of the administration of volatile acids in the food. They found that 0.2 to 0.5 gm. per kilo of acetic acid caused an increase of peristalsis usually with diarrhea and occasionally with vomiting. When less than the effective dose was given they noted a well-marked defensive effort on the part of the pylorus, the orifice opening much less frequently than normal and thus providing more time for the secretion of digestive juices to the extent necessary for neutralization of the acid entering the duodenum. In another series of experiments they administered the acids below the pylorus by injecting them through a duodenal fistula. Small amounts were injected at short intervals, mixed with chyme. The amounts of acetic acid needed to produce diarrhea by this method of experimenting was found to be 0.04 to 0.16 gm. per kilo, very much less than when the acid was given by mouth.

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[3] Holt, Courtney and Fales: Am. Jour. Dis. Child., 1915, **9,** 213.

[4] Bahrt and Bamberg: Ztschr. f. Kinderh., 1912, **3,** 322.

The concentration of free volatile fatty acid in sour milk and developing in the infant's stomach during digestion was then studied.[5] In sour milk the concentration of lower fatty acids (chiefly acetic) measured with tenth-normal NaOH was found to be 8 to 10 c.c. per 100 c.c., and in stomach contents (mostly butyric acid) 10 to 22 c.c. The fatty acids in the stomach were not found to be increased in dyspepsia with diarrhea. The concentration in sour milk was one-tenth and in the stomach contents one-fifth that needed to cause an increase in peristalsis in dogs when given by mouth. The authors conclude that if diarrhea is to be related to free volatile fatty acids it must be assumed that they are produced for the most part in the intestine itself; and here, as they have shown, a much lower concentration than in the food is effective because of the defense of duodenal alkalinity afforded in the latter case by the pyloric reflex. That there is a production of volatile acids in the intestine has been shown by stool analysis. Edelstein and Csonka[6] found, for instance, 0.7 gm. acetic acid and 0.125 gm. butyric acid in 100 gm. stool from a normal breast fed infant. That the volatile acids are produced chiefly through the agency of intestinal bacteria is shown by the relatively much larger amount of acetic than of butyric acid. The volatile acids cannot, of course, exert an effect on peristalsis unless they are free. Bahrt and McLean[7] have made an extensive study of the amounts of free and combined volatile fatty acids found in the stools of normal infants and of infants with diarrhea. They distilled altogether some 140 stools by the Edelstein-Weldeschen method.[6] Expressed as cubic centimeters of tenth-normal NaOH per 100 gm. stool, they found, in average, from stools of normal breast fed infants 22 c.c. free and 111 c.c. combined volatile acid. With various modifications of cow's milk there was found in stools from normal infants no free volatile acids (except with Friedenthal's milk, and in one of five instances with buttermilk). The amount of combined volatile acid was in average 90 c.c. The addition of sugar to breast milk doubled the amount of free volatile acid in the stools, but an increase in the sugar in the cow's milk modifications did not cause the appearance of free volatile acids in the stools. In a series of infants with "Dyspepsie," 21 per cent. of the volatile fatty acids were free when the food was breast milk, and 10 per cent. free when the infants received cow's milk. In examination of another series of stools from infants with severe "enterocatarrh," and in many instances presenting symptoms of "Intoxikation," there was found on breast milk 30 per cent. of the volatile fatty acids free, and on cow's milk, 38 per cent. free. The diarrheal stools from both "Dyspepsie" and "enterocatarrh" contained about the same total amount of volatile acids per 100 gm. fresh stool as was found in stools from normal infants. The absolute amount of volatile acids excreted must, however, have been much greater than normal, since in diarrhea the volume of the stool is two to six times normal. The authors believe that this large production of volatile acids may well tend to exceed the supply of base in the food and intestinal secretions. From their duodenal fistula experiments with dogs the authors are convinced that the 30 to 50 c.c. (tenth-normal NaOH) free volatile acids per 100 gm. stool found in "Dyspepsie" and "enterocatarrh" represents a concentration which if present in the small intestine of an infant would be much more than sufficient to cause an active increase in peristalsis, and they infer that the presence in the stools of such an amount of free volatile acids indicates that they exist in the small intestine in sufficient concentration to provide the immediate cause of diarrhea. They are, of course, unable to supply direct proof of their theory, and its correctness must be regarded as problematical. It is conceivable that in diarrhea a large part of the volatile acids could be produced in the large intestine and their presence in the stools represents a result rather than a cause of the condition. As regards the cause in the first instance of the "souring of the chyme," their evidence is against assuming an ingestion of free volatile acids or their production in the stomach in sufficient amount. They are inclined to regard a disturbance of the pyloric reflex as the initial cause of diarrhea. They suggest, for instance, that overfeeding might lead to an abnormally rapid passage of food into the small intestine and thereby supply the intestinal bacteria with an unusual amount of material from which it would be possible for them to produce acid to an extent in excess of available base.

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[5] Huldschinsky: Ztschr. f. Kinderh., 1912, **3,** 366.

[6] Edelstein and Csonka: Biochem. Ztschr., 1912, **42,** 372.

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[7] Bahrt and McLean: Ztschr. f. Kinderh., 1914, **11,** 143.

The authors wish also to relate chronic nutritional disturbances of the type of Czerny's "Milchnärschaden" to the presence in the intestine of the volatile acids. In this condition their concentration is not regarded as being so high as in "Dyspepsie," but is sufficient to cause an increase in peristalsis in the small intestine, which is indicated by a decreased fat absorption and an increased nitrogen excretion. The stimulus to peristalsis is, however, not strong enough to involve the large intestine, and the stool mass remains there long enough to permit the absorption of water, of the alkali salts, and the alkali present in combination with the higher fatty acids, which is replaced by calcium and magnesium supposed to be excreted into the intestine at this point. The stools resulting are typical, more or less dry "soap stools" containing more calcium and magnesium and very much less sodium and potassium than diarrheal stools. In diarrhea the stimulus to peristalsis is of such degree that the large intestine is also involved so that the stool mass does not remain there long enough to permit of salvage of the alkalies. The authors insist that the building of insoluble soaps which takes place in the large intestine in "Milchnärschaden" is only an incidental result of the condition. They and other workers have shown that the amount of higher fatty acids in soap stools is quite insufficient to bind all of the calcium and magnesium present and should not therefore be regarded as bearing a causative relation to the loss of these metals. They refer the loss of the earth alkalies to the increase in intestinal secretion and of persistalsis due to the presence of free volatile acids, resulting in the carrying into the large intestine of large amounts of sodium and potassium which are there saved at the expense of calcium and magnesium. The authors discuss the quantitative relation of the lower fatty acids to the base loss obtaining in diarrhea. From the values for volatile fatty acids obtained in their investigation of diarrheal stools they have calculated, using a one-half maximal figure, that the stool from one of the infants with severe "enterocatarrh" studied by Jundell[1] may have contained enough volatile acid to combine with 3 gm. of base (reckoned as K_2O). In this case of Jundell's $CaO + K_2O$ and Na_2O amounted to 1.2 gm. They conclude that there is probably a sufficient amount of volatile fatty acids present in diarrheal stools to bind all the base present. They maintain, however, that the cause of the base loss is not related to the base-claiming value of the volatile fatty acids, but to their effect in stimulating the secretion of alkali and preventing its absorption by increasing peristalsis.

A Specific Toxic Substance a Cause of Diarrhea?—The most recent effort to relate diarrhea to the presence in the intestinal canal of a particular toxic substance has been made by Mellanby.[8] He believes that a substance known as βimidozolyethelamine, and for which he suggests the abbreviation βi, may, with great probability, be held accountable for the more acute and severe types of diarrhea and vomiting in infants and children. This substance can be derived from the amino-acid histidin simply by the removal of CO_2, and is related to products of intestinal putrefaction such as cadaverin and putrescin, which are known as ptomains and are supposed to be capable of producing symptoms of food poisoning. βi was first isolated from ergot by Barger and Dale,[9] and they later demonstrated its presence in the alimentary canal of normal animals. The author is able to obtain βi from histidin by the action of a certain bacillus which can be isolated from the feces of human beings.[10] Experiments with animals have shown it to be capable of producing diarrhea and vomiting, fall of systemic blood pressure, depression of the respiratory center, coma and death. Mellanby has studied in cats the conditions which favor the absorption of βi from the intestinal canal. He found that the presence of food (milk or meat) or of water in the intestine greatly decreased the rate of absorption of the substance. Injection of large amounts of Ringer's solution into the circulation had the same effect. Absorption was most rapid from the empty intestine and was further increased when the water content of the body was reduced by bleeding. He found absorption of βi most rapid in the region of the cecum, and that apparently it was not taken up at all from the large intestine. He determined the relative concentration of βi in his samples of intestinal contents by finding the amount of the sample needed to produce a full contraction of a guinea-pig's uterus when added to Ringer's solution in which the uterus was suspended. He argues that the conditions which he found to favor absorption, namely, an empty intestine and a depletion of the water content of the body, are those presented by infants who have suffered from minor gastro-intestinal upsets, and that they are then liable to severe symptoms due to absorption of βi.

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[8] Mellenby: Quart. Jour. Med., 1915-1916, **9,** 164.

[9] Barger and Dale: Jour. Physiol., 1910, **40,** Proc. 37; ibid., 1910-1911, **41,** 499.

[10] Mellanby and Twort: Jour. Physiol., 1912-1913, **45,** 53.

CHRONIC DISTURBANCES OF NUTRITION

Energy Metabolism in Chronic Malnutrition.—Bahrt and Edelstein,[11] and Kurt and Wolff[12] have added to the rather small number of instances in which the energy exchange has been determined in conditions of chronic malnutrition. The infant used in the experiment of Bahrt and Edelstein was 8 months old and weighed 5 kilos. It had suffered a month previously from severe enterocatarrh, following which there was, on breast milk, a steady gain in weight, but when given a modification of cow's milk (⅔ whole milk and 5 per cent. sugar) the gain in weight became irregular and unsatisfactory. The authors define the condition of malnutrition at the time of the experiment as 'Bilanzstörung." The energy exchange was determined by means of a Pettenkofer-Voit respiration apparatus for two periods of four days each, with an interval of four days between. The infant was in the apparatus about twenty-two and one-half hours each day. The infant gained about 60 gm. during each period, which is a normal rate for an infant of 8 months, but is unsatisfactory when the infant is underweight. The nitrogen retention in average for both periods was 0.13 gm. per kilo per day, and about ⅐ of the nitrogen in the food (normal 0.08 gm. to 0.16 gm., or ⅙ to ¼ of intake). The nitrogen retention was therefore barely normal, but much less than would be retained if the previously lost tissue were being rebuilt at a proper rate. Nieman[13] found in the stage of repair following malnutrition a retention of 0.3 gm. per kilo per day, which amounted to 40 per cent. of the nitrogen intake. The energy exchange was nearly identical in both periods. In average for both, of the 121 calories per kilo per day contained in the food, which the authors regard as 60 per cent. more than the normal maintenance need, there was utilized by the organism 112 calories, and of this number 101 were spent in heat production, leaving 11 calories for processes of tissue building. In a normal infant about the same heat value is applied to growth and repair and very much less than 101 calories per kilo per day to actual heat production. Nieman[13] found in the stage of repair following "Atrophie," that 20 of 115 calories per kilo per day utilized by the organism were invested in tissue building, and Rubner and Heubner[14] found in a similar case that 25 of 114 calories were so spent. In both these cases the calories used in heat production were also markedly higher than normal. The authors chose for estimation of the surface area of their infant, Lissauer's modification of Meeh's formula. Their reasons for this choice are not obvious. Lissauer's modification gives a smaller surface area than Meeh's, which in itself contains the tendency, because of the weight factor, to underestimate surface area when applied to undernourished infants. As might be expected from their method of calculation, they obtained for their infant the highest yet recorded value for heat production per square meter of body surface — 1,711 calories. Recalculated by Meeh's original formula, the heat production was 1,475 calories. One thousand calories per square meter may be taken as a maximum average value for the heat production of a normal infant during quiet periods.[15] Bahrt and Edelstein claim that their malnourished infant was extremely quiet throughout the experiment. If this is true, its heat production was about 50 per cent. higher than normal.

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[11] Bahrt and Edelstein: Ztschr. f. Kinderh., 1915, **12,** 15.
[12] Kurt and Wolff: Jahrb. f. Kinderh., 1913, **78,** (Ergänzungsheft) 1.
[13] Nieman: Jahrb. f. Kinderh., 1911, **74,** 663.
[14] Rubner and Heubner: Ztschr. f. Biol., 1899, **38,** 315.

Kurt and Wolff measured the energy metabolism of a 4½-months-old infant that had suffered several acute digestive upsets and for some time preceding the experiment had gained only slightly in weight. An occasional rapid loss of weight, sometimes with fever, indicated the presence of a serious derangement of nutritional processes. At the time of the experiment the weight was 3½ kilos. They obtained two periods of four days each with an interval of a week between. The respiratory exchange was measured by a Pettenkofer-Voit apparatus. The food was protein milk with 4 per cent. sugar during the first period and 5 per cent. during the second. During the first period the infant gained 25 gm. and during the second, 70 gm. The stools were loose during the first day of each period, but in the subsequent days were typical "soap stools." That there was no appreciable disturbance of assimilation was suggested by the fact that the nitrogen absorbed was in both periods more than 90 per cent. of the nitrogen in the food. The nitrogen retention was in average of both periods 0.33 gm. per kilo per day, or 31 per cent. of the intake, which is considerably more than is retained by an infant in a normal state of nutrition. During the first period the caloric value of the food was 108 calories per kilo per day. During the second it was 115. The authors regard the caloric intake as 35 to 40 per cent. over the maintenance need of a normal infant. In spite of this apparently liberal supply of extra fuel, there was spent in the processes of metabolism during the first period more calories (123) than the food contained, with the result that 18.6 gm. of body fat were burned during the four days. During the second period the caloric consumption was 111 calories per kilo per day. The heat production per day per square meter of body surface (calculated by Meeh's formula) was, in the first period, 1,581 calories and in the second, 1,431, and was therefore, as in the infant studied by Bahrt and Edelstein, about one half more than periods 0.33 gm. per kilo per day, or 31 per cent. of the intake, which is the amount produced by healthy infants.

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[15] Benedict and Talbot: Am. Jour. Dis. Child., 1914, 8, 1.

The outstanding feature of the results of both of these experiments is the excessive heat production accompanying a chronic disturbance of nutritional processes. The specific dynamic action of protein can scarcely be held accountable for so large an increase in the expenditure of available energy as heat. In the experiment of Bahrt and Edelstein the protein intake was not excessive. The inappropriateness of protein milk as a food in chronic malnutrition is, however, indicated. In the experiment of Kurt and Wolff, the loss of heat by evaporation of water from the lungs and skin was 38 to 44 per cent. of the total heat production (normally 32 to 35 per cent. of the heat produced is so spent). Bahrt and Edelstein's infant lost 23 per cent. in this way. Apparently an anomaly in water metabolism cannot be regarded as a probable cause of the excessive heat production. Bahrt and Edelstein suggest that the extra heat produced must be due either to a primary inability of the organism to build tissue, or else to some cause directly increasing heat production. As regards the first possibility, they hint that a disturbance in the assimilation or subsequent metabolism of some small but essential (therefore probably mineral!) constituent of the food may be at the bottom of the trouble. As a cause for excessive heat consumption they suggest an overactivity of the digestive glands in response to some intra-intestinal stimulus. In view of our complete ignorance of the cause of the energy wastage in malnutrition, it would perhaps be more ingenuous to assume that when the nutritional machinery is out of kilter more heat must be spent in carrying out metabolic processes than when these processes are in exact adjustment.

Energy Metabolism in Absence of the Cerebral Hemispheres.—Talbot[16] determined the energy exchange in an 8-months-old infant in which during an operative search for the cause of its blindness the cerebral hemispheres were found to be absent. Although the infant weighed more than the normal average for its age, its muscular development was extremely poor. Lack of volitional muscular movement was apparently nearly complete. It made few and small movements unless directly stimulated by being touched. Its heat production during four periods in which the slight movements were least frequent, was, in average, 32 calories per kilo per day, and was therefore markedly lower than the average basal metabolism of normal infants (65 calories per kilo[15]). The author regards the low heat output per kilo as due to the relatively small protoplasmic mass within the body from lack of a proper development of muscular tissue by volitional exercise. In proportion to the size of its protoplasmic mass the heat production was in this infant probably normal.

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[16] Talbot, F. B.: Arch. Pediat., 1915, **32**, 452.

Chronic Malnutrition Due to Protein?—In spite of the nonsuccess of the many attempts which have been made to relate nutritional disturbances to the protein part of infants' food, Benjamin[17] challenges again its reputation for absolute harmlessness. From a lengthy consideration of the existing data and from results of some experiments of his own he is inclined to believe that a prolonged and excessive intake of cow's milk protein may lead to a state of chronic malnutrition characterized chiefly by a slowing of the rate of weight gain. The type of disturbance he describes resembles closely that which Czerny defined as "Milchnärschaden," and for the development of which an excessive amount of fat in the food has usually been blamed. His experiments consisted simply in a determination of the relation of retained nitrogen to gain in weight in a well, and in a malnourished infant. The experiments are unique in the length of period used. The results obtained are interesting, but their interpretation is not obvious, and the indictment of protein which he has devised from them is in the main fanciful. In his first experiment he determined the nitrogen balance in a "nearly normal" infant for closely successive periods of from three to seventeen days and extending from the age of five weeks to 3½ months. The sum of the periods gave a total of seventy days. A metabolism frame being obviously impracticable for such a plan of experiment, he devised a rubber napkin to receive the stools. The infant was given at first breast milk, then breast milk and an increasing amount of skimmed milk, and finally ⅔ whole milk and 5 per cent. sugar. On these three types of milk the average daily gain in weight was in order 16 gm., 24.1 gm., and 13.3 gm., and the average daily nitrogen retention, 0.6 gm., 1.1 gm., and 0.71 gm. Measured per unit of weight gained, the nitrogen retention showed a steady increase as the shift was made from breast milk to cow's milk. For 100 gm. of weight gained, the nitrogen retention was, on breast milk, 3.7 gm., on breast milk and skimmed milk, 4.5 gm., and on ⅔ whole milk and sugar, 5.3 gm. The last two milk mixtures contained nearly double the amount of nitrogen supplied by breast milk alone. With each addition to the nitrogen intake there was noted a rise, and then after a few days a subsidence, of the level of nitrogen retention. A similar experiment was carried out with a six-weeks-old infant that had been misfed since birth, and at the beginning of the experiment weighed only 2,060 gm. It was given breast milk and then breast milk and skimmed milk, the relative and absolute amount of the latter being gradually increased. The total of days during which the nitrogen retention was determined was fifty-seven. The average daily gain in weight was, on breast milk, 10 gm., on breast milk and skimmed milk, in moderate amount, 22.5 gm., and with the addition of more skimmed milk, 16.5 gm. The nitrogen retained daily was in order, 0.39 gm., 1.1 gm. and 1.2 gm. Per 100 gm. of weight gained there was a larger increase in the retention of nitrogen as the amount of cow's milk in the food was increased than was noted in the case of the well infant. On breast milk the nitrogen retained per 100 gm. increase in weight was 3.9 gm. As skimmed milk was added it rose to 4.9 and 7.1 gm. The rise in the level of nitrogen retention as the nitrogen intake was increased was fairly sustained. If the 3.7 gm. nitrogen retained by the well infant per 100 gm. of weight gained while receiving breast milk is multiplied by the usual factor, 29.5, the increase in "flesh" thus calculated is 109 gm. Similarly, in the case of the sick infant, while receiving breast milk the calculated gain in "flesh" is 115 gm., which quite fairly approximates the 100 gm. actual gain in weight. With the addition of cow's milk to the diet, and an increase in the nitrogen intake, the actual gain in weight became in both instances greatly less than the increase in "flesh" as calculated from the amount of nitrogen retained. The author regards the correspondence between weight gained and calculated "flesh" increase, obtaining when the infants received breast milk alone and when the nitrogen intake was relatively low, as indicating a normal "correlative" growth; meaning that the newly built tissue contains a normal amount of nitrogen. The "normal" infant, omitting a part of the experimental period during which dyspeptic symptoms were present, gained in weight in fifty-three days 890 gm. The nitrogen retained was 40.6 gm. According to Rubner and Heubner,[18] 0.186 gm. nitrogen may be lost daily in the sweat. Assuming in this case a loss of 0.1 gm. daily, and subtracting 5.3 gm. from the nitrogen retained, the estimated increase in body protein is 1,044 gm. — 154 gm. more than the increase in body weight. The sick infant gained in fifty-seven days 490 gm. and retained 64 gm. of nitrogen. Allowing more liberally in this instance for loss of nitrogen in sweat (0.2 gm. daily) the calculated increase in flesh was 1,550 gm., or more than three times the actual gain in weight. The author spends many pages in contemplation of the riddle of what becomes of the retained nitrogen which is not represented by an appropriate increase in body tissue. A loss of water from the body would permit an equivalent increase in body tissue which would not be indicated by an increase in weight. While admitting the fact that the water content of the tissues decreases as the age of the infant advances, he does not believe that this physiologic loss of water can be made accountable for more than a small part of the discrepancy between his actual and calculated figures for body increase. Water retention is known to be a widely fluctuant quantity, but he feels sure that the length of his experimental period rules out the effect of a temporarily low water balance. He does not mention the possibility of a gradual, more than normal, water loss from the malnourished infant, or the possibility of the change in the character of the food producing a change in the water content of the body. He is disinclined for vague reasons to regard a loss of fat as accountable in appreciable degree for his findings. He seems unnecessarily concerned over the possibility of some of the retained nitrogen being applied to repair instead of tissue growth, though it would seem in an experiment of such length that nitrogen used for repair would be covered by the presence in the urine of the effete nitrogen it replaced, and so would not count in the nitrogen balance. His experiments are well planned in point of duration, but whether or not the discrepancy he calculates between tissue increase and nitrogen retention is approximately actual must be regarded as problematical. He mentions that Grafe and Graham[19] encountered a similar dilemma in their study of the ability of the organism to accommodate to continued overfeeding. They found that a healthy dog on a high protein diet retained in fifty-nine days 298 gm. of nitrogen, although its weight, which was 20 kilos, remained stationary throughout the experiment. Benjamin concludes that his results show that a prolonged high intake of cow's milk protein, probably in well infants, and quite certainly in infants whose nutritional processes are already disturbed, leads to the presence in their tissues of an abnormally large amount of nitrogen. Whether the extra nitrogen forms inert deposits or is added to the normal nitrogen content of living protoplasm, its presence in the tissue cells must alter their chemical texture and may therefore with great probability be supposed to interfere with processes of cell metabolism. A slowing in the rate of the processes concerned in tissue building is an effect particularly suspected by the author. The good results obtained by treating chronic disturbances of nutrition of the type of Czerny's "Milchnärschaden" with malt soup he regards as due not to the low fat in this food, but to the small amount of protein present. It would seem that the author's theory of an overstuffing of the tissue cells with nitrogen might be easily tested directly by postmortem tissue analysis.

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[17] Benjamin: Ztschr. f. Kinderh., 1914, **10**, 185.

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[18] Rubner and Heubner: Ztschr. f. Biol., 1899, New Series, **37,** 18.

Organ Analyses in Chronic Malnutrition.—Klose[20] complains that a foundation of chemical facts has never been supplied for the use, in describing disturbances of nutrition, of terms, such as "Dekomposition," for instance, which imply a change in the chemical structure of the organism. The only work previous to his own done to determine the effect of chronic malnutrition on tissue composition is that of Steinert and Weigert.[21] These workers decided from the results of analyses of the bodies of our atrophic infants that, even with the presence of marked emaciation, the normal chemical texture of the tissues is preserved. Their belief is that wasting of body substance is a process in which tissue is lost in toto, and that in the living protoplasm remaining there is no alteration in the relative amounts of the various tissue constituents. Klose believes that such an inference cannot be safely made from the gross results of body analysis. He presents analyses from the individual organs of a 5-weeks-old infant. Before death the symptoms were those of "Mehlnärschaden" and there was marked edema. Figures for comparison were obtained from a new-born infant dying from obstetric trauma. The weights of the two infants were nearly the same — 3,000 and 3,200 gm. He found in the new-born 564 gm. fat and in the atrophic infant only 39 gm. For the body as a whole there was, in 100 gm. fat-free substance, from the new-born 82 gm. water, 14.5 gm. protein and 3.5 gm. ash. Corresponding figures for the atrophic infant were 86 gm., 10 gm. and 2.8 gm. Regarding the excess of water per gram of fat-free dried substance in the atrophic over that per gram of dried substance in the new-born as pathologic, the author estimates that the body of the infant with edema contained more than a liter (1,100 c.c.) of "pathologic" water; 50 per cent. of this extra water was found in the skin and 20 per cent. of it in the muscles. Of the total water content of the new-born, one fifth was found in the skin and one third in the muscles. In the infant with edema this distribution was nearly exactly reversed. The author mentions that in adults only 5 per cent. of the water content of the body is found in the skin and 50 per cent. is in the muscles. There was in the atrophic infant a slightly greater loss of nitrogen than of minerals, as shown by the fact that there was found per gram of nitrogen 1.8 gm. of ash as compared with 1.5 gm. in the new-born. This relatively greater loss of nitrogen is revealed especially in the skin and muscles. As regards the individual constituents of the ash, there was found more sodium and chlorin and less calcium, magnesium, and especially potassium, in the infant with edema than in the new-born. The increase in sodium and chlorin did not seem to be especially related to the water retention, since the increase was most marked in the muscles, whereas most of the extra water was found in the skin. The relative amounts of the various minerals in the skin, muscles and viscera was found to differ more or less from the proportions obtaining in the new-born. The ratio of calcium to magnesium in the muscles, for instance, was found to be the reverse of normal. The author concludes that the results of his chemical autopsy thoroughly disprove the theory of a "constancy of the relative composition of tissue" advanced by Steinert and Weigert.

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[19] Grafe and Graham: Ztschr. f. physiol. Chem., 1911, **73,** 1.
[20] Klose: Jahrb. f. Kinderh., 1914, **80,** 154.

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[21] Steinert and Weigert: Monatsch. f. Kinderh., 1905, **4**, 301.

ACIDOSIS

Keller,[22] in 1896, reported a marked increase in the "ammonia coefficient" (ammonia nitrogen to total nitrogen in the urine) in cases of severe nutritional disturbance in infants. In many instances he found more than 50 per cent. of the urinary nitrogen in the form of ammonia. He used the old and very inaccurate Schlösing method, and much of the ammonia he measured must have come from decomposition of urea. Nevertheless, the fact that the ammonia coefficient may be high in cases of disturbed nutrition has since been well substantiated. During the twenty years since Keller reported this finding there has been from time to time a great deal of discussion in the literature as to the source and significance of this increased urinary ammonia. Pfaundler[23] believed that in cases of malnutrition, as part of a general lowering of the oxidative ability of the tissues, the liver was unable to synthesize urea to the normal extent, but the early observation of Bergh,[24] who found that the ammonia could be made almost entirely to disappear from the urine by giving sodium bicarbonate, pointed strongly to the inference that the extra ammonia in the urine represented an unusual need on the part of the body to conserve its supply of fixed alkali, and this interpretation of the finding came to be the generally accepted one. Pfaundler himself later suggested the word "Alkalopenie" to describe the condition represented by an increase in urinary ammonia. Recent research has shown this term of Pfaundler's to be absolutely accurate. The term acidosis was frequently applied to the condition, but always with a certain diffidence because of the usual absence of the ketone acids which regularly accompany the high ammonia coefficient in diabetic acidosis. Search for other organic acids was unsuccessful.[25] Finkelstein made the easy assumption that the extra base was needed to neutralize acid products of bacterial fermentation absorbed from the intestine, but supplied no chemical facts in support of his view. Steinitz[26] by showing that infants receiving a milk high in fat lost an unusual amount of sodium and potassium in the stools (coincident with an increase in the ammonia in the urine), and the finding by other workers of a frequently negative mineral balance, especially for sodium and potassium, in diarrhea, led finally to a definite belief that a high ammonia coefficient, if unaccompanied by acetonuria, indicated a "relative" acidosis; that is, the acidosis was caused by a loss of base and not by the presence of abnormal acids, as in the "true" acidosis of diabetes. All of the work which supports this belief contains the fallacy pointed out by Howland and Marriott[27] that the loss of acid radicals was not determined and shown to be less than the loss of base. As regards the actual disability which the organism may suffer from such a "relative" acidosis, opinion has been entirely vague. All attempts to supply infants showing a high ammonia coefficient with a distinguishing set of clinical symptoms have been unsuccessful.[2] General opinion seems to have been to regard the "relative" acidosis as probably completely compensated for by the extra ammonia supplied by the body at the expense of urea, and not in itself a serious condition. This is evidenced by the single fact that there has been no tendency to treat the condition by giving alkali. Czerny[28] alone suspected correctly that the deep breathing which he observed in certain cases of severe diarrhea was related to a serious disturbance of the acid-base equilibrium within the body. He was led to this inference because of the resemblance of the type of respiration to that shown by rabbits poisoned with mineral acids.

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[22] Keller: Jahrb. f. Kinderh., 1897, **44,** 25.

[23] Pfaundler, M.: Jahrb. f. Kinderh., 1904, **60,** 719.

[24] Bergh, van den: Jahrb. f. Kinderh., 1897, **45,** 265.

[25] Statement by Steinitz: Monatsch. f. Kinderh., 1902, **1,** 225.

[26] Steinitz: Jahrb. f. Kinderh., 1903, **57,** 689.

The mechanism by means of which the neutrality of the blood is maintained has been uncovered for us with wonderful clearness by the work of L. J. Henderson.[29] Recently, methods have been devised for testing directly the efficiency of the parts of this mechanism. The presence of a condition which may correctly be called acidosis need therefore be no longer a matter of uncertain inference, based, for instance, on the presence of the ketone acids, or of an unusually large amount of ammonia in the urine. It is a regular function of ammonia to save alkali for the body. A high ammonia coefficient merely means an unusual need for alkali conservation, but does not in itself afford ground for supposing that the body's store of fixed alkali is actually reduced. As regards the acetone bodies, the neutrality mechanism is capable of an adjustment which will manage the conveyance of large amounts of these abnormal acids into the urine without depletion of the normal alkali content of the blood. It is therefore absolutely improper to regard the presence of acetone bodies in the urine as proof of a disturbance of the acid-base balance within the body. With our new knowledge and methods, the terms acetonuria and acidosis need no longer be jumbled. By acidosis we understand an embarrassment of the neutrality mechanism due to a less than normal alkali content of the blood and of such degree that it has caused the reaction of the blood to slip slightly in the direction of acidity. The increase in the hydrogen ion concentration in the blood is always extremely small. A shift from the normal slightly alkaline reaction to only so far as neutrality is not compatible with life. The increase in acidity is usually so small that it cannot be directly measured by our present methods. The respiratory center, however, is sensitive to an almost infinitesimal increase in the hydrogen ion concentration in the blood and promptly and definitely indicates its presence by causing an increased ventilation of the alveolar air spaces. This response of the respiration center is visible clinically as hyperpnea and is demonstrable chemically by the finding of a lower than normal CO_2 tension in the alveolar air, due to the dilution of the alveolar air produced by the extra ventilation. The physiologic purpose of the lowering of the CO_2 tension in the air spaces is to produce a corresponding decrease in the carbonic acid content of the blood in effort to restore there the normal ratio between acid and base which is disturbed in acidosis by a reduction of the blood's fixed alkali content. The presence of an acidosis can therefore be definitely shown by finding, (1) a lower than normal CO_2 tension in the alveolar air or in the blood, or (2) a lower than normal alkali content of the blood or, (3) an increase in the hydrogen ion concentration of the blood.

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[27] Howland and Marriott: Am. Jour. Dis. Child., 1916, **11**, 309.

[28] Czerny: Jahrb. f. Kinderh., 1897, **45**, 271.

[29] For a summary see Henderson: Ergebn. d. Physiol., 1909, **8**, 254.

Using the most recent methods, Howland and Marriot[27] have shown with great thoroughness that infants with diarrhea may develop an actual and extremely dangerous acidosis. The urine of these infants does not contain acetone bodies in significant amount. The only clinical symptom which regularly accompanies the acidosis and is a reliable guide to its presence is deep breathing — hyperpnea — accomplished by vigorous use of the thoracic as well as of the diaphragm muscles. With the help of an ingenious mask they were able by the Plesch method to collect, for the first time from infants, alveolar air samples. In a series of normal infants they found the carbon dioxid tension to vary from 36 to 45 mm. In infants severely sick with diarrhea and showing hyperpnea, the carbon dioxid tension was always below 30 mm., often below 20 mm., and in one instance was only 14 mm. By a simple method which Marriott[30] has devised they were able to demonstrate a well-marked reduction of the alkali content of the blood serum in these cases. The method consists in blowing out the carbon dioxid from the serum and then reading the hydrogen ion concentration by the indicator method of Levy, Rowntree and Marriott.[31] After removal of the volatile fraction (carbon dioxid) of the acid content of the blood its reaction will necessarily shift in the direction of alkalinity, and the shift will be large or small according as there is much or little base present. They found that normally the reaction of the serum after removal of the carbon dioxid is, using the logarithmic notation for hydrogen ion concentration, between 8.4 and 8.5. In their cases of diarrhea with hyperpnea it ranged from 8.1 to 7.5. (In the logarithmic notation the numerals decrease as the hydrogen ion concentration increases.) Testing the serum directly, without first removing the CO_2, they were able to measure by the indicator method, in some of their cases, an actual very slight increase in the hydrogen ion concentration. In normal infants the reaction of the serum was never more than 7.4. In diarrheal cases with hyperpnea they several times found the hydrogen ion concentration increased to 7.2. They were also able to show indirectly but more strikingly the presence of an actual increase in the hydrogen ion concentration of the blood by testing the oxygen combining power of its hemoglobin by the method of Barcroft.[32] Barcroft has determined that if normal blood is exposed to an oxygen tension of 17 mm., in the absence of CO_2 the hemoglobin becomes 70 to 80 per cent. saturated; but that if the acidity of the blood is very slightly increased, much less oxygen is combined. Howland and Marriott found that blood from their cases of diarrheal acidosis became, when exposed to a tension of 17 mm. of oxygen, only 15 to 25 per cent. saturated. The evidence advanced by Howland and Marriott to show that a dangerous acidosis may be present in diarrhea is remarkably complete and definite, and as it supplies an obvious therapeutic indication — the administration of alkali — the finding is one of immense usefulness. The cause of the reduction of the alkali content in the blood in these cases is at present entirely obscure.

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[30] 30. Marriott, W. McK.: Arch. Int. Med., 1916, Part 1, **17,** 840.

[31] 31. Levy, Rowntree and Marriott: Arch. Int. Med., 1915, **16,** 389.

ACETONURIA

That the acetone bodies are regularly present in small amounts in the urine of normal infants and children has been repeatedly shown. Langstein and Meyer[33] found 1 to 4 mg. in twenty-four hour urines from infants, and in older children 3 to 10 mg. Liefman[34] gives approximately the same figures. Veeder and Johnson[35] have recently examined the urines from twenty-one normal infants and children for acetone and diacetic acid, and for beta-oxybutyric acid using the more recent method of Schaffer. They found a much larger amount of acetone bodies than had been previously reported. Expressed as acetone, the average daily excretion was 50 to 80 mg. Slightly more than half was usually in the form of beta-oxybutyric acid. Hüssy[36] obtained an enormous increase in acetone excretion in children by placing them on a fat and protein diet. The acetone in the urine increased rapidly and in several instances amounted to more than a gram on the second day of the diet. Other observers have also found that infants and children are much more liable to an acetonuria from carbohydrate deficiency in the diet than are adults. It has been suggested that the reserve supply of carbohydrate in the younger organism is relatively small. L. Meyer[37] measured a quite considerable increase in acetone excretion in acute infectious diseases. In measles and scarlet fever he found as much as 140 mg., and in diphtheria 160 mg. He assumes the increase to be due to inanition and probably more directly to an insufficient carbohydrate intake. That there is very frequently an increase in the acetone excretion in infants and children beyond the amount which may be called physiologic has been well indicated by Howard.[38] He examined the urine from 171 consecutive patients suffering from various minor ailments and found that in thirty-one instances there was enough acetone present to make positive the rather insensitive sodium nitroprussid test. Digestive upsets and acute infections of a not very serious type, such as tonsillitis, coryza, otitis media and bronchitis were the conditions most often accompanied by a positive acetone test. Metcalf,[39] in studying a curious epidemic among infants and children in Concord, Mass., in which the symptoms suggested food poisoning, found acetone present in all of the cases (100) in which the urine was examined. Acetonuria may apparently be regarded as a disease symptom occurring in infancy and childhood nearly as frequently as fever. The assumption, however, that its presence always indicates a dangerous defect in metabolism, namely, acidosis, is quite unjustifiable. The papers of Metcalf and Howard, and others which might be cited, bear in their titles the word acidosis, but contain no evidence to show that the acid-base balance in the body is actually disturbed by the presence of these abnormal acids. The fact that the ferric chlorid test was negative in two of Metcalf's five fatal cases would suggest that the ketone acids were probably not present in an amount sufficient to embarrass the neutrality mechanism, and that these children quite certainly did not die of acidosis.

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[32] Barcroft: The Respiratory Function of the Blood, 1914, Cambridge.

[33] Langstein and Meyer: Jahrb. f. Kinderh., 1905, **61,** 438.

[34] Liefman: Jahrb. f. Kinderh., 1913, **77,** 125.

[35] Veeder and Johnson: Am. Jour. Dis. Child., 1916, **11,** 291

PERIODIC VOMITING

Very little investigative work in this condition has appeared in recent years. An experiment of Hilliger's[40] may be described. The

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36. Hüssy: Zentralbl. f. d. ges. Physiol. u. Path. d. Stoffwechs., 1906, **1,** 5.
37. Meyer: Jahrb. f. Kinderh., 1905, **61,** 438.
38. Howard: Boston Med. and Surg. Jour., 1915, **172,** 747.
39. Metcalf: Am. Jour. Dis. Child., 1915, **9,** 28.
40. Hilliger: Jahrb. f. Kinderh., 1914, **80,** 1.

subject was a 6-year-old girl suffering from quite typical attacks of periodic vomiting. The author's chief point is that he was able to induce attacks by lowering the carbohydrate portion of the diet. He gave a normal diet containing 36.5 protein, 52 gm. fat, and 160 gm. carbohydrate, and on this found that the acetone bodies in the urine amounted to 4 to 5 mg. daily. An addition of 100 gm. fat to this diet caused a scarcely appreciable increase in acetone excretion (5.9 mg.); but when the carbohydrate intake was reduced by half — to 75 gm. — the acetone in the urine rose on the same day to 134 mg., on the next day to 640 mg., and on the day following fell to 423 mg. On the fourth day the acetone in the urine was again the normal amount. During the three days that the acetone in the urine was high the child suffered a vomiting attack with typical symptoms. A diet similarly low in carbohydrate was given to several normal children, but did not cause an increase in acetone exretion. The experiment was repeated on the susceptible subject and a nearly identical increase in the acetone excretion for a period of three days was obtained. This time the blood sugar was determined each day by the Bang micromethod and was found on the second day of the attack to be decreased by one half. The figures for blood sugar on the three successive days of the attack were 0.13, 0.07 and 0.13 gm. per 100 c.c. The amount of acetone in the urine during these days was 175, 620 and 200 mg. On the second day of the attack the vomiting and other symptoms were most severe. The author points out that the symptoms abated and the acetone in the urine came down to normal before the usual carbohydrate intake was restored (the child took almost no food during the three days), and that therefore the attack cannot be referred to an insufficiency in the body of stored carbohydrate. His interpretation, based on the finding of a low sugar content of the blood on the second day, is that the demand for the release of carbohydrate from its storage depots created by the insufficient carbohydrate intake, is less quickly met than is normally the case. As soon as the sugar mobilization mechanism gets under way and supplies the processes of intermediary metabolism with a proper amount of carbohydrate, as indicated by the presence of a normal amount of sugar in the blood on the third day, all evidences of metabolic disturbance disappear. The author's theory is ingenious and interesting, but rests rather heavily on a single blood sugar determination.

RICKETS

In spite of numerous and laborious investigative attempts, not the slightest hint of the character of the error in metabolism which causes the condition of rickets has yet been obtained. All feeding or gland extirpation experiments have yielded negative results or have led only to the production of the ubiquitous osteoporosis — a condition in which bone is more or less empty of calcium, but does not present histologically a trace of the changes which are characteristic of rickets. As regards calcium metabolism in rickets, little more has been learned than might be expected from the histologic picture. The calcium content of rachitic bone is much lower than in normal bone. Schabad found, for instance, that ribs from normal infants contained 22 to 25 gm. CaO, whereas in ribs from rachitic infants there was 4 to 17 gm. CaO. Aschenheim[41] analyzed for calcium the ash of blood obtained postmortem from rachitic children and found a widely variable Ca content, ranging in a series of seventeen cases from 3.7 to 12.8 mg. CaO per 100 c.c. of blood. In a series of normal infants he found a fairly constant value of 8 to 10 mg. per 100 c.c. He interprets his findings as meaning that in rickets calcium is lost from the bones and turned into the blood at an irregular rate. Katzenellenbogen,[42] using the micromethod of Wright, by which the amount of ionized calcium in the blood is roughly indicated by determining the amount of ammonium oxalate which must be added to the blood to prevent its clotting, could not find that the Ca content of the blood in any of the stages of rickets differed from that in the blood of normal infants. A reliable method for measuring calcium in the ash of small blood samples has been at last supplied by Marriott and Howland.[43] Using this method they found in three samples from placental blood, and in the blood of six normal infants and three adults, a remarkably constant amount of calcium.[44] Except in one instance, the amount of Ca per 100 c.c. of serum was between 9.8 and 11.3 mg. They examined blood from eleven infants under 1 year of age showing clinically evidence of active rickets, and found that in some of the cases the calcium in the blood was slightly reduced, but in no instance did they find less than 9.0 mg., and in five of the cases the Ca content was more than 10 mg. Aschenheim and Kaumheimer[45] have recently shown that the amount of calcium in the muscles of rachitic children is less than normal. Numerous experiments have shown that in the florid stage of rickets the amount of calcium daily retained is nearly always below the average normal figure of 0.17 gm. CaO, supplied by Orgler.[46] Not infrequently the Ca balance is negative. The immediate suggestion of the lowered Ca balance, that rickets might be due to a primary calcium insufficiency, as might occasionally happen in breast fed infants, or to a secondary insufficiency due to an interference with calcium absorption, by excessive formation of soap stools for instance, seems unlikely, since in all experiments in which these conditions have been imitated the only result has been the occasional production of an osteoporosis. The low or negative calcium balance is therefore much more probably due to some defect in its intermediary metabolism which prevents its deposition in bone tissue. The amount of calcium retained increases, and often becomes much higher than normal, during the healing stage of rickets. The administration of codliver oil, calcium salts and preparations of organically combined calcium have been found to cause an increase in calcium retention. They may therefore be fairly regarded as remedial agents. Whether their effect is to cause an increased absorption of calcium or in some way to mend the defect in its intermediate metabolism, is not apparent. Schloss[47] has recently completed a long series of laborious experiments in which he determined the effect on calcium retention in rachitic children of the administration of cod liver oil and of calcium preparations, alone and together. The effect was tested in infants on breast milk, on a milk high in fat, and on protein milk. His results in average from a series of eighty experiments were as follows: Calcium retention in the fore-period was 0.032 gm. CaO per day. Cod liver oil alone produced an average daily retention of 0.167 gm. Calcium preparations alone gave a retention of 0.297 gm. daily. When both cod liver oil and calcium preparations were given, the average daily retention of CaO was 0.354 gm. He gave the cod liver oil with and without phosphorus without being able to notice a difference in its effect on calcium retention. Tricalcium phosphate caused a slightly better retention than calcium acetate and was equally as efficient as various preparations containing organically combined calcium. In a number of his experiments he measured also the retention of the other minerals, sodium, potassium and magnesium. It has been noticed that as the calcium retention increases in healing rickets the retention of sodium and potassium falls and may become negative. From this a relation of the alkaline minerals to rickets has been inferred, and the observation has also been much mentioned as an instance of an "antagonism" which is supposed to exist between the metabolism of the earth alkalies and of the alkaline minerals. Schloss was able to show that the reduction of Na and K retention is probably due merely to an interference with their absorption, caused by the stimulus to peristalsis provided by cod liver oil. He found that when protein milk, which prevented this effect of cod liver oil, was given there was no disturbance of alkali retention. He also made the interesting observation that during the florid stage of rickets there was in some instances an abnormally high magnesium retention, which fell rapidly to a low or negative value during the healing stage, and as the calcium retention increased. He is, however, in doubt as to whether this finding may not in some way be related to the medication given.

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[41] Aschenheim: Jahrb. f. Kinderh., 1914, **79,** 446.

[42] Katzenellenbogen: Ztschr. f. Kinderh., 1913, **8,** 187.

[43] Marriott, Howland and Haessler: Jour. Biol. Chem., 1916, **24,** Proc., **18.**

[44] Howland and Marriott: Tr. Am. Ped. Soc., 1916, **28,** 200.

[45] Aschenheim and Kaumheimer: Monatsch. f. Kinderh., 1912, **10,** 435.

[46] Orgler: Ergebn. d. inn. Med. u. Kinderh., 1912, **8,** 166.

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[47] Schloss: Jahrb. f. Kinderh., 1915, **82**, 435.

OSTEOGENESIS IMPERFECTA

The metabolism of calcium in this condition has been studied by several workers. Schwarz and Bass[48] found in a 7-months infant an average daily retention of 0.109 gm. CaO. In a 3-months infant, Bamberg and Huldschinsky[49] found in average 0.042 retained daily. An average from three periods during which the infant received cod liver oil and phosphorus gave a daily retention of 0.089 gm. Bookman,[50] studying an infant of the same age, found a daily retention of 0.054 gm. CaO and was able to increase the retention to 0.402 gm. by giving calcium lactate in the food. Orgler[46] gives the daily retention of CaO in normal infants as ranging from 0.13 to 0.21 gm. CaO. The results of the experiments just cited suggest that calcium retention is somewhat low in osteogenesis imperfecta during infancy, and that an increase in retention may be obtained by giving calcium salts (evidence of a single period obtained by Bookman). Schabad[51] determined the calcium balance in an older child in twelve six-day periods between the ages of 7 and 10 years. There was unfortunately only one period without medication; this gave a calcium balance of 0.176. Two periods with phosphorus and cod liver oil gave a balance of 0.340. In a period during which she received calcium acetate and cod liver oil the daily retention was 0.338 gm., but for another period with the same medication the balance was slightly negative. Two periods in which thyroid extract was given, gave in one a low (0.047 gm.) and in the other a slightly negative balance. During two periods with Fowler's solution there was retained 0.403 gm. and 0.382 gm. Herbst[52] found in a normal child of this age 0.418 CaO retained daily. Schabad concludes that calcium retention is low in osteogenesis imperfecta and can be best restored to normal by giving arsenic. His results, however, give the impression strongly that the amount of calcium retained varied widely and probably without relation to the kind of medication given.

TETANY[53]

Because of the frequent association of tetany with rickets, investigation early took the direction of attempts to show a disturbance of calcium metabolism. Stoeltzner,[54] from feeding experiments in which he gave calcium salts, decided that tetany was due to an increase in the calcium content of the tissues. This view is probably the mirror image of the truth in the matter. Numerous experiments have failed to show that a negative or decreased calcium balance occurs with any regularity in tetany. Quest,[55] however, found the calcium content of the brains of two infants with tetany very considerably lower than that of the brain of a normal infant. Assuming the nitrogen content to be constant, he found that the ratio N : Ca was in the brain from the normal infant 164, while in the brains from the spasmophilic infants the quotient was 240 and 269. Ramacci[56] and Silvistri[57] also found less than the normal amount of calcium in brains from spasmophilic children. M. Cohen,[58] however, was not able to confirm this finding. Pollini[59] found in analysis of the ash of blood obtained postmortem from three cases of tetany, 2.0, 2.7 and 3.8 mg. of CaO per 100 c.c. The blood of his single control patient, however, contained only 2.3 mg. These figures are far below the average for normal infants — 8 to 10 mg. — supplied by Aschenheim.[41] Katzenellenbogen,[42] using the micromethod of Wright, which measures roughly the ionized calcium in the blood, found on examining the blood of five infants with tetany that in four of them the method occasionally indicated that there was less than the normal amount of calcium present. Definite information on this point has been very recently supplied by Howland and Marriott.[44] They used a micromethod for ash analysis devised by themselves and found the calcium content of the blood in tetany to be regularly low. In seven cases with active symptoms the Ca content of the blood was found to be 5.0 to 6.5 mg. per 100 c.c., except in one instance in which it was 7.3. In a case in which tetany was latent, that is, was indicated only by the presence of characteristic electrical reactions, there was found in the blood 8.5 mg. Ca. In one of the cases which gave, during the presence of active symptoms, a Ca content of 6.0 mg., there was subsequently found, after the disappearance of all evidences of tetany, 10.4 mg. Ca. In blood samples from five normal infants the amount of Ca was found to lie between 10.8 and 11.5 mg. per 100 c.c. They found also in tetany in dogs following removal of the parathyroids, a decrease in the calcium content of the blood. In one instance, before operation the Ca in the blood was 10.8 mg., and forty-eight hours after parathyroidectomy was 7.3 mg. In another experiment the Ca content before operation was 10.0 mg., and twenty hours after was 8.9. Six days after the operation it had fallen to 6.8 mg.

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[48] Schwarz and Bass: Am. Jour. Dis. Child., 1913, **5**, 131.

[49] Bamberg and Huldschinsky: Jahrb. f. Kinderh., 1913, **78**, (Ergänzungsheft), 241.

[50] Bookman: Am. Jour. Dis. Child., 1914, **7**, 436.

[51] Schabad: Ztschr. f. Kinderh., 1914, **11**, 230.

[52] Herbst: Jahrb. f. Kinderh., 1912, **76**.

[53] For fairly recent reviews of literature of tetany see Rye: Arch. Pediat., 1914, **31**, 664, and Aschenheim: Jahrb. f. Kinderh., 1914, **79**, 446.

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[54] Stoeltzner: Jahrb. f. Kinderh., 1906, **63**, 661.
[55] Quest: Monatsch. f. Kinderh., 1911, **7**.
[56] Cited by Aschenheim, note 53.
[57] Cited by Aschenheim, note 53.
[58] Cited by Aschenheim, note 53.
[59] Cited by Aschenheim, note 53.

The finding by physiologists that certain mineral ions exert a specific effect on nerve muscle irritability has greatly stimulated investigation of the cause of tetany. J. Loeb[60] designates nerve muscle irritability as a function of the quotient Na ÷ Ca; Na tending to decrease and Ca to increase the threshold for excitation. The ion K has been credited with the same property in this respect as Na, whereas Mg has been shown by Melzer to exert a depressant effect similar to that of Ca. Neuromuscular hyperirritability would therefore seem to be due to a disturbance in the balance normally maintained between the antagonistic effects of the earth alkali ions Ca and Mg on the one hand, and the alkali ions, Na and K on the other, and in the direction of producing an abnormal preponderance of the specific effect exerted by the alkalies. The effect of administration of salts containing these various mineral ions in the condition of tetany has been tested by a number of workers. Rosenstern[61] was able to demonstrate in children with tetany a reduction of electrical irritability after giving large amounts of calcium salts by mouth; and after giving 6 to 8 gm. of NaCl he thought that an aggravation of the tetanoid condition could be observed. He noted an improvement when whey was withdrawn from the diet. Zybell[62] was also able to reduce slightly electrical irritability in tetany by giving large amounts of calcium salts, and to increase it by giving a single dose of 3 gm. of potassium acetate. Grulee,[63] using smaller doses of calcium, obtained no effect. Berend[64] finds that injection of magnesium sulphate reduces electrical hyperirritability and relieves carpopedal spasm. MacCallum and Voegtlin[65] found that, in the case of dogs with tetany produced by parathyroidectomy, the injection of calcium or of magnesium salts stops the tetanoid symptoms, whereas the injection of sodium or potassium salts tends to increase their severity. This latter effect is, however, not so clear cut as the opposite one exerted by Ca and Mg. If the theory that the hyperirritability in tetany is due to a preponderance of the specific ion effect of the alkalies, Na and K, over that exerted by the earth alkalies, Ca and Mg, is accepted, it may be assumed that the alkalies are absolutely increased, or that they are only relatively in excess, due to the presence of a less than normal amount of Ca + Mg in the tissues. In favor of the latter view is the finding of Quest that the Ca content of the brains of spasmophilic children is low. This has been confirmed by Cooke and others. McCallum and Voegtlin found the amount of calcium in the brain, spinal cord and blood of dogs with parathyroid tetany abnormally low. They speak of tetany as "calcium diabetes." Very definitely to the point is the low calcium content of the blood of infants with tetany, recently shown by Howland and Marriott. Unfortunately, nothing is known quantitatively of the metabolism of magnesium in tetany. Aschenheim,[66] although he found a less than normal amount of calcium in the brains of spasmophilic children, claims, however, that there is also an absolute increase (Stauung) of the alkalies in the brain tissue. He is inclined to relate tetany to an abnormally high sodium and potassium retention and advocates a complete removal of whey from the milk for relief of the condition. Lust[67] describes the case of a child of 2 years with marked edema and tetany, which disappeared when the edema was relieved, and infers that the tetany was due to an increased NaCl retention. This observation of Lust has led Brown and Fletcher[68] to formulate a theory of the cause of tetany which refers the condition to an increase of Na and K in the tissues, due to an increased water retention which has been brought about by overfeeding with carbohydrate. They also regard constipation as an important factor in causing an abnormally high retention of the alkaline minerals, arguing this inversely from the relatively large loss of Na and K, as compared with Ca and Mg, in diarrheal stools shown by Holt, Courtney and Fales.[3] In support of their theory they present the results of a single experiment with a 13 months infant with tetany. They determined the retention of Na, K, Ca and Mg for two five-day periods. During the first period the infant was extremely constipated and the twenty-four hour amount of urine was less than 200 c.c. Before and during the second period a diuresis was produced by the administration of urea by mouth, the twenty-four hour amount of urine increasing to 600 c.c. The infant was less constipated during the second period, electrical irritability was much lower and carpopedal spasm had disappeared. In the second period as compared with the first, there was a decrease in the amount of K_2O retained, 0.2202 as against 0.4464 gm. and a marked increase in the retention of MgO, 0.0706 gm. as compared with 0.0032 gm. in the first period. The amounts of Na_2O and CaO retained were practically the same in both periods; the figures for Na_2O were 0.143 gm. and 0.145 gm., and for CaO, 0.3896 gm. and 0.4389 gm. There was therefore, an increase in the earth alkalies and a decrease in the alkalies in which sodium did not share. How the authors construe their results to support the view that tetany is caused chiefly by an unusual retention of sodium and

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[60] Cited by Rye, note 53.
[61] Rosenstern: Jahrb. f. Kinderh., 1912, **62,** 154.
[62] Zybell: Jahrb. f. Kinderh., 1913, **78,** 29.
[63] Grulee: Am. Jour. Dis. Child., 1913, **5,** 205.
[64] Berend: Monatsch. f. Kinderh., 1913, **12,** 269.
[65] MacCallum and Voegtlin: Jour. Exper. Med., 1909, **11,** 118.

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66. Aschenheim: Monatsch. f. Kinderh., 1910, **9**, 366.
67. Lust: München. med. Wchnschr., 1913, **6**, 93.
68. Brown and Fletcher: Am. Jour. Dis. Child., 1915, **10**, 313.

potassium is not obvious. Whether or not tetany should be referred to a disturbance of function in the parathyroid gland is a difficult point and remains unsettled. The physiologic and chemical findings in tetany in infants and in experimental animals after parathyroidectomy are nearly identical. Histologic evidence is, however, quite definitely negative as regards an association of the parathyroid with tetany in infancy, but it is of course not permissible to conclude from the absence of morphologic change that there can be no disturbance of chemical function.

Quite new and interesting chemical findings in tetany after parathyroidectomy have recently been reported by Wilson and co-workers.[69] They have shown that in dogs after removal of the parathyroids there develops a disturbance in the acid-base balance in the body to the extent of causing a shift in the reaction of the blood in the direction of alkalinity. The condition which results may therefore be termed alkalosis. They demonstrated its presence very thoroughly by finding an increase in the carbon dioxid tension in the alveolar air, an increased saturation of hemoglobin with oxygen and also by measuring directly a slight decrease in the hydrogen ion concentration in the blood. Additional evidence was obtained by determining a decrease in the titratable acid, ammonia, and hydrogen ion concentration in the urine. All of this evidence of alkalosis disappeared during the periods of acute tetany, probably because of the production of lactic acid accompanying the muscular spasms. The alkalosis could be made to disappear by the injection of hydrochloric acid. They made also the extremely interesting observation that the injection of calcium salts not only relieves the symptoms of tetany, as was shown by McCallum and Voegtlin, but also that following its administration there is a change in the reaction of the blood in the direction of acidity, as shown by a decreased combining power of hemoglobin for oxygen and a lowering of the tension of carbon dioxid in the alveolar air, just as is obtained after the injection of acid.

SCORBUTUS

Bahrt and Edelstein[70] analyzed the ash of the bones and organs from an 8 months infant dying with scorbutus. They found in the bones one fifth to one third as much calcium as normal, and a parallel decrease in the amount of phosphorus. This finding is identical with that which obtains in rickets, and, moreover, they found, as in rickets, a low calcium content in the muscles. For the results of their alkali analyses of bones, good comparison figures are lacking, but the authors believe that the amounts of sodium and potassium found were at least as much as normal. The bones contained one half as much dried substance as normal, and two to three times as much water. They are inclined to regard the figures obtained from analysis of the ash of the viscera as probably normal, although satisfactory data for comparison does not exist. The authors refrain from stating definitely that the infant was not rachitic.

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[69] Wilson, Stearns and Thurlow: Jour. Biol. Chem., 1915, **23**, 89. Wilson, Stearns and Janney: Jour. Biol. Chem., 1915, **21**, 169, and 1915, **23**, 123.

[70] Bahrt and Edelstein: Ztschr. f. Kinderh., 1913, **9**, 415.

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THE NONPROTEIN NITROGEN OF THE BLOOD IN ATROPHIC INFANTS *

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The purpose of our work was the determination of the nonprotein nitrogen of the blood of infants, particularly of infants suffering from disorders of nutrition of the severer types. The blood was taken in quantities of 3 to 5 c.c. from the longitudinal sinus, following the directions of Helmholz.[1] The poor condition of most of our atrophic infants was the reason for taking as small quantities of blood as possible. In most of the cases the total nonprotein nitrogen and the urea nitrogen were determined, the former according to the method of Folin and Denis,[2] the latter by the Van Slyke and Cullen[3] modification of Marshall's[4] method. The portion of the alcoholic filtrate of the blood which is used for the determination of the urea nitrogen must be taken before the addition of zinc chlorid, because this substance interferes with the urease action. Creatin and creatinin were determined in a few of our normal and pathologic cases according to the method of Folin[5] as modified by Myers and Fine.[6] We found 1.1 to 1.6 mg. creatinin nitrogen and 3.0 to 7.6 mg. creatin nitrogen per 100 c.c. of blood, these figures agreeing well with those found in the table of Veeder and Johnston,[7] but subject to the criticism of Hunter and Campbell,[8] as our picric acid solution was old and not protected from light. In a few cases the amino-acid nitrogen was determined according to Van Slyke.[9] In four cases of our normal series and in five of the atrophic infants we found 3.5 to 7 mg. nitrogen per 100 c.c. of blood, figures agreeing with those obtained by Pettibone and Schlutz.[10]

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* From the Otho S. A. Sprague Institute Laboratory of the Children's Memorial Hospital.

1. Helmholz, H. F.: Am. Jour. Dis. Child., 1915, **10,** 194.
2. Folin and Denis: Jour. Biol. Chem., 1912, **11,** 527.
3. Van Slyke and Cullen: Jour. Am. Med. Assn., 1914, **62,** 1558.
4. Marshall: Jour. Biol. Chem., 1914, **17,** 351.
5. Folin: Jour. Biol. Chem., 1914, **17,** 475.
6. Myers and Fine: Chem. Composit. of the Blood, etc.
7. Veeder and Johnston: Am. Jour. Dis. Child., 1916, **12,** 136.
8. Hunter and Campbell: Jour. Biol. Chem., 1916, **28,** 335.
9. Van Slyke: Jour. Biol. Chem., 1915, **13,** 407.
10. Pettibone and Schlutz: Jour. Am. Med. Assn., 1916, **67,** 262.

Table 1 gives the results of total nonprotein and urea nitrogen determinations in mg. per 100 c.c. of blood. The sixteen infants, so-called feeding cases, were all doing well. The determinations were made before feedings, the infants being fed on mixtures of cow's milk at four-hour intervals. In most cases duplicate determinations were made, at least of the total nonprotein nitrogen, the duplicates agreeing rather well in most instances (cf. table). In Cases 6, 13 and 15 the difference exceeds 2 mg. It was not always possible to make duplicates of the urea nitrogen determinations, but where made, the agreement was quite good.

TABLE 1.—Convalescent Feeding Cases

No.	Name	Date	Age, Mos.	Wt., Lbs.	Mg. Total Nonprotein Nitrogen per 100 C.c. Blood		Mg. Urea N per 100 C.c. Blood	Remarks
1	Nel. O.	12/28/15	1	5.2	22.0	....	7.4	Discharged improved, 1/18/16
2	Tom. J.	3/ 3/16	2	7.0	23.6	23.6	11.5	
3	Florence Z.	2/18/16	3	9.10	26.2	26.0	....	Before a meal
	Florence Z.	....	...	.....	27.9	27.5	....	After a meal
4	Tom. J.	4/10/16	3	8.6	23.0	23.0	12.1	Discharged; doing well
5	Kline F.	2/26/16	3	5.4	22.0	21.3	13.0	Premature; doing well
6	John K.	4/15/16	3	6.4	25.7	23.0	11.0	Discharged; doing well
7	Vernon G.	6/ 3/16	4½	7.13	24.8	24.5	13.5	Improved; doing well
8	James B.	12/21/15	5	8.6	23.0	22.4	....	Discharged; doing well
9	Elmer D.	3/18/16	5	11.3	25.9	25.2	13.1	Doing well
10	Bridget L.	12/18/15	6	10.2	23.4	21.8	14.4	Discharged; doing well
11	Magdalene G.	3/14/16	6	6.4	27.0	26.0	12.6	Discharged; doing well
12	Leon T.	4/20/16	6	10.8	24.3	....	....	Discharged; going well
	Leon T.	6/ 5/16	8	11	21.6	20.2	10.2	Discharged; doing well
13	Jos. N.	4/14/16	8	11.13	26.8	24.6	13.6	Discharged; doing well
14	Amelia P.	6/22/16	8	10.9	24.0	....	12.1	Discharged; doing well
15	Helen S.	6/13/16	10	10.10	24.0	21.4	8.8	Discharged; doing well
16	Malvina G.	2/24/16	16	12.8	20.0	18.2	11.0	Before a meal
	Malvina G.	....	...	.....	27.3	26.3	12.0	After a meal

There is no uniformity of opinion in regard to the normal limits of the total nonprotein nitrogen of the blood in adults. Folin and Denis give 22 to 26 mg. per 100 c.c. of blood as the normal. Folin, Denis and Seymour,[11] Tileston and Comfort,[12] Frothingham and Smillie,[13] Rowntree, Marshall and Baetjer,[14] and others accept as normal values those given by Folin and Denis,[2] or values varying between 20 and 30 mg. Others, as, for instance, McLean and Selling,[15] say the normal varies from 23 to 36 mg. Of greater interest to us here are the determinations in younger individuals. Schlutz and Pettibone[16] found in 9 infants from ½ hour to 10 days of age, 23 to 40 mg.; Veeder and Johnston, working on normal children from 2 to 14 years of age, get 22 to 33 mg. (5 exceeding 30 mg.); Leopold and Bernhard[17] get 19 to 40 mg. in 50 patients free from renal involvement, but suffering from various other diseases; the ages varied from 2 to 13 years; in 21 cases the total nonprotein nitrogen exceeded 30 mg. All these investigators used the method of Folin and Denis. Greenwald[18] objects to the use of alcohol in the precipitation of the blood, because the precipitate carries with it amino-acids and does not precipitate some lipoid nitrogen. In his determinations on 6 normal individuals, by the method of Folin and Denis and by his modification, he invariably finds higher values for the total nonprotein nitrogen by his method. In two instances his values exceed 30 mg. (31.0 and 31.7 mg.). Gettler and Baker[19] use hydrochloric acid and mercuric chlorid for the precipitation of the proteins. In their 30 patients, ranging from 17 to 60 years of age, they get from 27 to 52 mg. per 100 c.c. of blood, according to their table. Bang,[20] using his own method, not given in his paper, in 42 individuals got from 19 to 39 mg. The age of the individuals varied from new-born to 82 years. Although he gives 25 mg. as the average value, he got values greater than 30 mg. in 9 cases.

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[11] Folin, Denis and Seymour: Arch. Int. Med., 1914, **13,** 224.

[12] Tileston and Comfort: Am. Jour. Dis. Child., 1915, **10,** 278; ibid., Arch. Int. Med., 1914, **14,** 620.

[13] Frothingham and Smillie: Arch. Int. Med., 1914, **14,** 541.

As Gettler and Baker[19] remark, the values for normal individuals given in the literature disagree more or less, and this may be due to the different methods used by the various workers, to the nature of the food or the time after a meal that the blood is taken. But quite aside from these factors is another very important one, namely, the latitude of the term "normal" individual. On the basis of our results we have been naturally very much inclined to accept as normal for the total nonprotein nitrogen of infants' blood, 22 to 30 mg. when determined by the Folin and Denis method. While our babies were doing well on nontherapeutic foods, they were convalescent from disorders of nutrition, and were, with few exceptions, decidedly underweight. *Sensu strictiori,* they are not normal, nor are many of the so-called normal

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14. Rowntree, Marshall, Baetjer: Arch. Int. Med., 1915, **15,** 543.
15. McLean and Selling: Jour. Biol. Chem., 1914, **19,** 31.
16. Schlutz and Pettibone: Am. Jour. Dis. Child., 1915, **10,** 206.
17. Leopold and Bernhard: Am. Jour. Dis. Child., 1916, **11,** 432.
18. Greenwald: Jour. Biol. Chem., 1915, **21,** 61.
19. Gettler and Baker: Jour. Biol. Chem., 1916, **25,** 211.
20. Bang: Biochem. Ztschr., 1915, **72,** 104 and 119.

cases of other investigators, not even some of those of Gettler and Baker. It is not at all impossible that a somewhat more guarded selection of individuals may aid in doing away with the greater discrepancies.

In two of our cases (3 and 6) the determinations of the nonprotein nitrogen were repeated after feeding, Case 3 perhaps showing a slight, Case 6 a definite, increase similar to the cases of Tileston and Comfort,[12] who found an increase after a heavy meal of meat. Bang's[20] work on animals and man shows similar results.

Table 2 contains the results we obtained in atrophic infants arranged according to the amount of nonprotein nitrogen found. All these cases belong to a severe type of decomposition. With the exception of Cases 2 and 9, the urine did not show any of the ordinary pathologic changes; the urine of these two children contained pus. Of the 26 cases, 15 had more than 30 mg. nonprotein nitrogen per 100 c.c. of blood, and 11 had less than 30 mg. Of the 15 patients with more than 30 mg., 12 died and the other 3 did poorly when they left the hospital. Of the 11 cases of atrophy with less than 30 mg. nonprotein nitrogen, 3 patients died, 6 did fairly well or well, and 2 poorly. In our series of observations it is certainly a striking feature that of the 15 patients who died, 12 had a nonprotein nitrogen over 30 mg. and of these, 9 over 35 mg., while 3 fatal issues fell to the share of the group with less than 30 mg. nonprotein nitrogen. The occurrence of a relatively high nonprotein nitrogen in our cases may be the result of the interplay of a variety of factors, such as retention or overproduction in relation to the water economy of the organism. For instance, Bang,[20] in his animal experiments, has shown that starvation leads to a very marked increase in the nonprotein nitrogen, and particularly of the urea nitrogen, provided no water is given. Veeder and Johnston report one case of starvation with a rather scant increase of the nonprotein nitrogen (31 to 35 mg.). Bang mentions a loss of water by the blood in cases of starvation. We have not sufficient data to enter into a detailed discussion of the possible explanations of the relatively high nonprotein nitrogen in our cases. Only in a few cases did we determine the number of red cells and hemoglobin in order to detect a possible marked concentration of the blood. Such determinations were made on Cases 4, 7, 17, 23 and 24 — the first two having a relatively high nonprotein nitrogen, the last two a relatively low nonprotein nitrogen. In no case was the red count above 4,000,000 and the hemoglobin was always low. Aside from these determinations, the similarity of the cases with high or low nonprotein nitrogen does not speak in favor of a concentration of the blood as a factor in the production of the high nonprotein nitrogen, although the final decision must be left to a special investigation of this point. The possible influence of substances summarized in the total nonprotein nitrogen on the course of the disease will have to be considered in the future.

TABLE 2.—ATROPHIC INFANTS

No.	Name	Date, 1916	Age, mos.	Wt., Lbs.	Wt. Curve	Lect. T.	Mg. Total Nonprotein Nitrogen per 100 C.c. Blood		Mg. Urea N per 100 C.c. Blood	Remarks
1	Harold Ne.	3/17	2	5.8	S*	96.5	58.4	58.0	34.3	Died 4/6/16
2	Louise K.	4/16	9	10.2	L	99.0	52.4	52.0	29.5	Pus in urine; died 4/23
3	Regina M.	5/15	3	6.3	S	97.0	51.6	48.8	37.0	Died 6/17
4	Mazie M.	1/15	1	4.3	L	98.0	43.0	....	20.2	Died 2/7
5	Rosie C.	5/29	5	7.14	G	97.0	38.6	37.0	23.0	Died 7/17
6	Tom Mc.	4/12	3	6.7	L	96.0	38.0	37.3	21.8	Died 5/23
7	Esther W.	3/10	2½	6.3	G	97.0	37.4	36.0	16.0	Died 3/27
8	Louise H.	4/ 8	10	6.13	S	96.0	37.0	37.0	21.5	Died 4/16
9	John P.	4/17	4	7.4	S	100.0	36.0	....	15.5	
	John P.	5/10	5	7.2	S	98.0	31.7	....	15.0	Pus in urine; improved, 6/17
10	Mollie F.	2/25	7	6.10	L	97.0	35.3	34.7	17.6	
	Mollie F.	7/18	12	6.12	L	98.0	38.8	....	20.3	Died 7/18
11	Rose P.	7/17	5	8.2	G	97.0	34.8	33.0	20.0	Doing poorly 7/30
12	Beverley G.	2/12	4	5.3	S	96.0	34.0	29.4	12.7	Died 3/1
13	Richard S.	3/15	2	5.12	S	97.0	33.3	32.8	10.0	
	Richard S.	5/18	4	5.12	S	98.0	29.7	....	10.4	Doing poorly 7/5
14	Fred W.	1/31	3	6.10	L	97.0	32.4	....	15.9	Died 2/19
15	Walker W.	1/24	8	7.12	L	97.0	30.7	....	....	Died 1/30
16	Myrtle D.	6/ 2	7	6.12	L	97.0	29.7	29.0	10.0	Died 6/19
17	John S.	5/13	8	7.12	S	100.0	29.0	24.9	8.0	
	John S.	5/27	8½	8.4	G	98.0	26.7	....	10.8	Doing fairly well 6/8
18	Harold Na.	4/19	8	7.9	L	96.0	26.9	26.4	12.3	Died 4/23
19	Ray S.	12/30	6	7.12	L	97.0	25.2	24.8	12.0	Died 1/8
20	Alice T.	6/28	8	9.0	S	98.0	24.8	22.6	10.8	Doing fairly well 7/14
21	Helen M.	7/12	2½	5.6	S	98.0	24.3	22.8	13.6	Doing poorly 7/30
22	Harry B.	4/26	6	6.10	G	97.0	23.1	....	8.9	Doing well 7/15 (9 pounds)
23	Robert S.	3/10	2½	6.0	S	98.0	23.0	20.6	6.1	
	Robert S.	4/29	4	7.8	S	98.0	19.5	19.3	5.6	
	Robert S.	5/ 3	...	7.8	S	100.0	21.2	....	7.7	Doing well 6/20
24	Helen S.	5/ 1	5	5.4	S	99.0	22.6	....	7.6	Doing poorly
25	Nellie O.	12/28	1	5.2	S	96.0	22.0	....	7.4	
25	Nellie O.	4/23	5	5.3	S	96.0	25.0	....	7.7	Doing fairly well 7/1
26	Louise K.	7/11	3	5	G	97.0	21.5	21.3	7.3	Doing well 7/28

* S = weight curve stationary when blood was taken; L = losing weight; G = gaining weight.

With reference to the relationship of the urea nitrogen to the total nonprotein nitrogen, Table 3 gives a survey of our series of cases. A is calculated from Table 1, leaving the figures obtained after feeding out of consideration. B is calculated from those cases of Table 2, wherein the nonprotein nitrogen exceeds 30 mg., and B2 from the remainder of Table 2, using in Cases 23 and 25 the averages for the calculation.

TABLE 3.—Summary of Authors' Cases

	Nonprotein N	Urea N	Nonprotein N Minus Urea N
A (16 cases).................................	24	12	12
B (15 cases).................................	39	20	19
B2 (11 cases).................................	25	10	15

It is a rather precarious undertaking to utilize averages from a relatively small number of cases which show quite extensive variations. We will, therefore, not dilate on the possible significance of these figures any further than to point out that the burden of the increase of the nonprotein nitrogen does not seem to be borne preponderantly by the urea nitrogen.

Another circumstance may be of significance: Where a relatively low nonprotein nitrogen was associated with an urea nitrogen markedly below 50 per cent. of the nonprotein nitrogen, the infants were, on the whole, getting on rather well (of Cases 17, 22, 23, 24, 25 and 26, only Case 24 did poorly). If such an occurrence should prove to be a concomitant feature of certain phases of the reparation from disorders of nutrition, it could easily explain the low urea nitrogen of Cases 1 and 15 of Table 1.

TABLE 4.—Alimentary Intoxication

No.	Name	Date	Age, Mos.	Wt., Lbs.	Mg. Total Nonprotein Nitrogen per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Remarks
1	John O.	2/12/16	13	21.0	67.6	31.7	Died 2/13; Temp. 106
2	Eugene A.	3/17/16	5	14.10	60.0 57.5	48.3	Died 3/18; edema
3	E. Smith	2/20/16	7	15.4	25.6	11.0	Feeding case; discharged well, 3/2/16
	E. Smith	4/ 5/16	8½	11.0	53.0	37.2	Died 4/7
4	John J.	4/21/16	4	9.9	29.4	16.1	Died 4/24
5	Leon C.	7/13/16	12½	17.2	28.0 27.2	18.4	Died 7/19
6	Loren H.	2/27/16	9	13.14	26.7 26.4	17.3	Died 3/1

Table 4 contains the results obtained in some cases of alimentary intoxication.

The urines of all the patients contained albumin and casts, so that in the cases with high nonprotein nitrogen (Cases 2 and 3) a renal insufficiency may play its rôle. Case 3 is of interest. When the infant was in the hospital the first time, suffering with a mild disturbance of nutrition, its nonprotein nitrogen and urea nitrogen were about normal. Six weeks after its discharge it returned in a state of acute alimentary intoxication, when its values were high. In all but one of our cases of intoxication the urea nitrogen was decidedly more than 50 per cent. of the total. The blood of the first three children was obtained within twenty-four to forty-eight hours before death; in the other cases it was obtained at least three days before death.[21]

CONCLUSIONS

1. The blood of infants recovering from the milder intestinal disorders contains between 20 and 30 mg. of nonprotein nitrogen per 100 c.c. as determined by the method of Folin and Denis, agreeing with the values obtained by several authors for normal individuals. The urea nitrogen forms about 50 per cent. of the nonprotein nitrogen.

2. In atrophic infants the nonprotein nitrogen frequently exceeds 30 mg. per 100 c.c. of blood, and these findings seem to be associated rather frequently with a bad prognosis.

3. A low urea nitrogen associated with a low nonprotein nitrogen in atrophic infants seems to be a favorable sign.

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[21] Dumitrescu and Popescu (Zentralbl. f. Biochem. Biophys., 1915, **18**, 184. Abstr., Chem. Abstr., 1916, **10**, 931) described a very marked increase of the total nonprotein nitrogen and urea in the blood shortly before death in patients suffering for some time of disease other than renal. The original paper is not at our disposal and the abstract does not contain any further data of use to us in this connection. Among some determinations in various conditions we have one made on an infant of 9½ months, weighing 16 pounds, which died of a capillary bronchitis on the day the determination was made. The nonprotein nitrogen was 24 mg., the urea nitrogen 13 mg., that is, there was no increase.

THE NITROGEN PARTITION IN THE URINE OF NORMAL CHILDREN *

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From time to time the need has arisen in our hospital work of having figures for the nitrogen partition in the urine of normal children, as a basis for comparison with figures obtained from patients with pathologic conditions. While there is no reason to presuppose that such figures would vary grossly from those for the nitrogen partition in the adult, in many respects children form a distinct group of individuals in so far as their metabolism is concerned. As evidence of this we might cite the increased total energy requirement of the infant and young child, the increased nitrogen retention coincident with growth and development, and the variations in the metabolism of some of the individual nitrogenous substances, as creatinin.

Previous studies of the nitrogen metabolism in children have been concerned with other phases, as for example the utilization of nitrogen and studies on the nitrogen requirements carried out on an individual child over a long period of time. In our problem we are concerned only with the distribution of the total nitrogen in the urine under normal or usual conditions.

DIET

In outlining the study the question of diet and its influence at once arose. It was decided to carry out the work in two parts. In one, a group of children were to be studied who were on a diet corresponding to the usual diet which a healthy child receives. For the second part, a study of the urine of children on a "creatinin-free" diet, and one which could be regulated according to body weight, was outlined. The second gives a better basis for comparative studies.

In outlining the diet for the first group a number of children were watched to see about how much food was taken when they were allowed a free supply, and the amount and proportion taken noted. Fixed quantities by age periods were then determined, and by actual test it was found that these were satisfactory both to the child and from the standpoint of maintaining body weight. We were surprised to note the large protein component in the diet of the average child.

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* From the Department of Pediatrics, Washington University Medical School, and the St. Louis Children's Hospital.

* Read before the Annual Meeting of the Central States Pediatric Society, St. Louis, Oct. 18, 1916.

The diet as outlined approximates very closely the diet of the healthy child under average economic circumstances. The diets outlined in this way we term "standard diets," and are as follows:

Diet for Children Between 20 and 36 Months of Age

6 a. m.	250 c.c. milk	Caloric value about 1,000, of which F = 40 to 45% C = 35 to 40% P = 15 to 20% 42 gm. protein—6.7 N
10 a. m.	Oatmeal * 250 c.c. milk	
2 p. m.	2 graham crackers 250 c.c. milk	
6 p. m.	1 slice zweibach 1 soft boiled egg 250 c.c. milk	

Milk refused during day to be saved and given at night.

Age 3 to 6 Years

Morning	Milk, 250 c.c. Oatmeal * 1 egg	Protein furnishes about 20% of calories Protein 52.6 gm. = 8 gm. nitrogen
Midday	Beef stew † Bread, 25 gm. Butter, 10 gm. Milk, 200 c.c.	(may be added to stew)
Evening	Bread, 25 gm. 1 egg Butter, 5 gm. Milk, 250 gm.	

Age 6 to 10 Years

Morning	Milk, 250 c.c. Oatmeal * 1 egg	Protein about 58 gm. = 9 gm. nitrogen
Midday	Beef stew ‡ Bread, 50 gm. Butter, 10 gm. Milk, 200 c.c.	(If child refuses butter on bread put in stew.)
Evening	Bread, 25 gm. Butter, 5 gm. Milk, 250 c.c.	

Age 10 to 14 Years

Morning	Milk, 250 c.c. Oatmeal * 1 egg Bread, 25 gm. Butter, 5 gm.	Protein equivalent to about 60-65 gm., or nitrogen about 10 gm.
Midday	Beef stew Bread, 50 gm. Butter, 10 gm. Milk, 25 c.c. Stewed prunes (5)	
Evening	Bread, 50 gm. Butter, 10 gm. Milk, 250 c.c. Eggs, 1	

* Oatmeal: 25 gm. oatmeal, 500 c.c. water; boil in double boiler four hours. Of this use 70 gm. oatmeal mixed with 10 gm. sugar, 5 gm. butter.

† Beef Stew: Stew 50 gm. lean beef cut fine, 30 gm. raw potato cut fine, 5 gm., salt q. s., 250 c.c. cold water; boil thirty minutes and serve entire portion.

‡ Beef Stew: Take 75 gm. lean beef cut in small pieces, add 40 gm. raw potato, 5 gm. butter and salt q. s., 300 c.c. cold water and boil. (Take off cover last five minutes.) Serve entire portion.

For the study of the nitrogen partition on a creatinin-free diet, a diet was devised in which the amount of nitrogen could be more definitely regulated than by a method of age periods, and one which at the same time was free of creatinin. After some experimentation the following diet was devised. It can be given over five- and six-day periods, and is fairly well liked by the children, except for the monotony. A few children were nauseated and vomited after the second day, and so the diet was not as satisfactory as desired. Such children were not utilized for the study.

Whole milk	200 c.c.
Cream, 20 per cent	200 c.c.
Two eggs	
Malted milk	200 gm.
Water to 1,000 c.c.	2 gm.

Each 100 c.c. contains approximately 150 calories; 35 to 40 calories per kilo of body weight are given and the total amount for the day is divided into five portions. Water is allowed freely as desired.

Each 100 c.c. contains approximately: fat, 7.5 gm.; protein, 6 gm.; carbohydrate, 15.5 gm.

METHOD OF STUDY

The method of study was as follows: Each child was placed on a diet as outlined in the foregoing, according to age in Group 1, and according to weight in Group 2, for a period of six days (occasionally five). No urine was collected the first two days. On the third and succeeding days the urine was carefully collected in twenty-four-hour periods. As a rule, no examination was made of the urine of the third day, but the urines of the fourth, fifth and sixth days were analyzed. A few times the urine of the third day was utilized in place of the specimen of the sixth day.

Determinations of total nitrogen were made by the Folin[1] micro-Kjeldahl method, of ammonia by the Folin[2] method, of uric acid by Benedict's[3] modification of the Folin method, of urea by the urease method of Van Slyke,[4] of creatinin and creatin by the Folin[5] method. In a previous paper we have published the results of acetone and betahydroxybutyric determinations on some of the specimens of urine collected for this study.[6] In all, six twenty-four-hour specimens were analyzed.

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[1] Folin and Farmer: Jour. Biol. Chem., 1912, **11,** 493.

[2] Folin and Macallum: Jour. Biol. Chem., 1912, **11,** 523.

[3] Benedict and Hitchcock: Jour. Biol. Chem., 1915, **20,** 619.

[4] Van Slyke and Cullen: Proc. Soc. Exper. Biol. and Med., Dec. 17, 1913.

[5] Folin: Jour. Biol. Chem., 1914, **17,** 469.

[6] Veeder and Johnston: Am. Jour. Dis. Child., 1916, **11,** 291.

TABLE 1.—NITROGEN PARTITION BY GRAMS AND PERCENTAGE FOR TWO CHILDREN ON A STANDARD DIET (Group 1)

Date and Age	Amt.	Sp. Gr.	Total Nitrogen	Ammonia Nitrogen	Urea Nitrogen	Creatinin Nitrogen	Creatin Nitrogen	Uric Acid Nitrogen	Per Cent. of Total Nitrogen					
									Urea	Ammonia	Creatinin	Creatin	Uric Acid	Undetermined
I. 21 mo.														
10/27–28	750	1.012	4.480	0.173	3.941	0.050	0.037	0.060	87.8	3.9	1.1	0.8	1.3	5.1
10/28–29	550	1.018	4.425	0.176	3.852	0.047	0.027	0.050	87.0	4.0	1.1	0.6	1.1	6.2
Average	650	1.015	4.45	0.175	3.897	0.049	0.032	0.055	87.4	3.9	1.1	0.7	1.2	5.7
II. 9 yrs.														
11/ 9–10	440	1.030	7.936	0.354	.....	0.165	0.112	0.069	....	4.5	2.1	1.4	0.9	
11/10–11	410	1.030	8.064	0.325	6.717	0.162	0.098	0.052	83.5	4.0	2.0	1.2	0.6	8.7
Average	425	1.030	8.000	0.340	6.717	0.164	0.105	0.060	83.5	4.2	2.0	1.3	0.8	8.2

RESULTS. STANDARD DIETS

In order to avoid the confusion of too many figures we will give first a detailed result of the analyses of the urine in two children, and then the average percentage partition for the entire group. Table 1 shows the figures obtained in a child of 21 months and in a child of 9 years.

TABLE 2.—Percentage Distribution of the Nitrogen in the Urine of Children on a Standard Diet

Age	Amt. 24 Hours	Total Nitrogen	Per Cent. of Total Nitrogen						Nitrogen Intake
			Urea	Ammonia	Creatinin	Creatin	Uric Acid	Undetermined	
19 months	845	4.43	85.8	6.5	1.2	0.6	2.0	3.9	6.27
21 months	650	4.45	87.4	3.9	1.1	0.7	1.2	5.7	6.71
24 months	480	3.72	81.0	8.5	1.0	1.1	1.4	7.0	6.71
34 months	640	4.88	87.7	4.2	1.0	0.9	1.1	5.1	6.71
4 years	550	6.69	86.0	4.1	1.4	1.0	1.0	7.5	8.10
4 years	690	7.67	85.0	3.5	1.3	1.5	1.2	7.5	8.10
7 years	440	6.26	78.5	5.9	2.1	1.5	1.4	10.6	9.25
9 years	335	5.78	83.0	4.5	2.1	0.5	1.7	8.2	9.25
9 years	425	8.00	83.5	4.2	2.0	1.3	0.8	8.2	9.25
10 years	980	11.50	86.5	3.2	0.8	2.2	1.0	6.4	10.16
10 years	775	7.30	82.0	4.6	2.2	1.9	1.2	8.1	10.16
12 years	435	8.13	82.0	3.7	2.7	1.3	1.3	9.0	10.16
11 years	710	7.22	81.5	3.7	2.3	1.3	1.5	9.7	10.16
Average	...	....	83.7	4.6	1.6	1.2	1.3	7.6	

In Table 2 the figures represent the percentage distribution of each of the nitrogenous substances studied.

They were obtained by averaging the figures for each child obtained by analysis of the daily specimens. It is difficult to get young children to cooperate in metabolic studies, and so we found that the daily variations in the amount of total nitrogen is at times considerable, but the relative amounts of different substances remain practically the same. By averaging the figures for several consecutive days the actual twenty-four-hour partition is obtained with a fair degree of accuracy.

RESULTS WITH CREATININ-FREE DIET

In Table 3 two instances are likewise given of the figures obtained in individual cases from children on the second diet (creatinin-free), in which the quantity given is regulated by the body weight of the child.

TABLE 3.—NITROGEN PARTITION BY GRAMS AND PERCENTAGE FOR TWO CHILDREN ON CREATININ-FREE DIET (Group 2)

Date and Age	Amt. 24 Hrs.	Sp. Gr.	Total Nitrogen	Ammonia Nitrogen	Urea Nitrogen	Creatinin Nitrogen	Creatin Nitrogen	Uric Acid Nitrogen	Per Cent. of Total Nitrogen					
									Urea	Ammonia	Creatinin	Creatin	Uric Acid	Undetermined
I. 28 mo.														
11/29-30	860	1.007	3.968	0.214	3.332	0.049	0.079	0.089	84.0	5.4	1.2	2.0	2.2	5.2
11/30-12/1	700	1.012	3.347	0.259	2.778	0.045	0.064	0.099	83.0	7.7	1.3	1.9	2.9	3.2
12/ 1-2	705	1.014	3.676	0.213	3.120	0.052	0.074	0.077	85.0	5.8	1.4	2.0	2.1	3.7
Average	755	1.011	3.663	0.229	3.077	0.049	0.72	0.088	84.0	6.3	1.3	2.0	2.4	4.0
II. 6 yrs.														
11/29-30	770	1.013	4.975	0.205	4.041	0.081	0.064	0.081	81.0	4.1	1.6	1.3	1.6	10.4
11/30-12/1	1140	1.007	4.800	0.213	3.760	0.100	0.038	0.101	78.3	4.4	2.1	0.8	2.1	12.3
12/ 1-2	610	1.013	4.733	0.200	.....	0.095	0.024	0.073	....	4.2	2.0	0.5	1.5	
Average	840	1.011	4.836	0.201	3.90	0.092	0.042	0.083	80.0	4.2	1.9	0.9	1.7	—

TABLE 4.—Showing Percentage Distribution of the Nitrogen in the Urine of Children on a Creatinin-Free Diet

Age	Amt. 24 Hours	Total Nitrogen	Per Cent. of Total Nitrogen						Nitrogen Intake
			Urea	Ammonia	Creatinin	Creatin	Uric Acid	Undetermined	
29 months	755	3.66	84.0	6.2	1.3	2.0	2.4	4.1	3.58
36 months	670	3.48	82.5	4.0	1.7	0.9	2.5	8.4	4.0
6 years	840	4.84	80.0	4.3	1.9	0.9	1.9	11.0	4.37
8 years	465	5.39	86.4	2.7	1.7	1.5	2.0	5.7	6.55
8 years	450	4.56	80.8	4.8	2.4	0.7	2.4	8.9	5.76
9 years	660	4.24	87.0	4.0	2.1	1.0	1.9	4.0	4.70
10 years	860	6.32	85.8	4.0	2.7	0.3	2.9	4.3	6.55
14 years	755	5.89	83.5	3.1	2.6	1.1	1.5	8.2	8.35
Average	...	....	83.7	4.1	2.0	1.0	2.2	7.0	

In Table 4 the average percentage distribution of the nitrogen in the urine is shown for eight children of different ages, in whom the nitrogen partition was studied on the creatinin-free diet. These figures were obtained in the same way as those in Table 2.

In all but two of the children studied there was a positive nitrogen balance which, as a rule, was rather large. The two children with a negative balance were very well nourished. In the group on the creatinin-free diet in which the nitrogen was proportionate to the body weight of the child, and the protein furnished 15 per cent. of the calories, the positive balance was smaller and more uniform, due to the smaller nitrogen intake.

TABLE 5.—Comparison of Creatinin-Free and Standard Diet Groups

	Urea	NH_3	Creatinin	Creatin	$Cr_1 + Cr_2$	Uric Acid
"Cr_1-free" diet group............	83.7*	4.1	2.0	1.0	3.0	2.2
Standard diet group.............	83.7	4.6	1.6	1.2	2.8	1.3

* Figures represent per cent.

Despite the marked difference in the diet in the two groups, the percentage partition of the nitrogen is strikingly similar, as is shown by comparing the averages of the two groups.

The only marked difference in the percentage distribution between the two groups lies in the amount of uric acid, which was considerably less in the urine of the children on the standard diet.

Urea and Ammonia.—It is interesting to note that in both groups the percentage of urea nitrogen is the same. On the creatinin-free diet the minimum and maximum figures are 80 and 87, respectively, and on the standard diet, 78.5 and 87.7. In only one instance was the amount under 80 per cent. The average figure is 83.7 per cent., which is somewhat less than the average of 87.5 per cent. obtained by Folin in studies on adults.[7] It must be taken into consideration that the method of determining the urea differed in the two studies. The decrease in the percentage of urea is not due to an increased percentage of ammonia nitrogen, as the figures for ammonia nitrogen, 4.1 and 4.6, respectively, in the two groups are approximately the same as the figure (4.3 per cent.) for adults. The difference is due to an increase in the amount of undetermined nitrogen. The ammonia percentage in the urine of children shows a wider range of fluctuation from the mean than in adults, but as a whole, the majority of the figures come very close to the average figure. As increased ammonia nitrogen is usually at the expense of the urea nitrogen, it is interesting to note that the combined urea + ammonia N figure averages about 88 per cent., or under 90 rather than above 90, as is the case in the adult.

Creatin and Creatinin.—The well known observation that creatin is found in the urine of children is borne out by our studies. It was found in every case, although some of the children were approaching puberty, and on an average formed a little over 1 per cent. of the total nitrogen. Little if any decrease occurred in the older children.

Relatively, the amount of creatinin is not as large as in the adult. It averaged about 2 per cent. of the total nitrogen in the children on a creatinin-free diet and a little less than that on a standard diet. In adults about 3.5 per cent. of the total nitrogen is in the form of creatinin nitrogen. This figure is more nearly approached by the combined creatin N + creatinin N figure. We noted a tendency for this combined figure to increase with age (body weight), and it is quite constant in a given individual from day to day. We know that in adults the creatinin elimination on a creatin-creatinin-free diet is quite constant both daily and hourly, but is not constant in relation to body weight, although this is a determining factor in the creatinin elimination.[7] In the urines studied the creatin N + creatinin N figure seems to bear a more definite relation to body weight, averaging between 7 and 8 mg. per kilogram with the child on a creatin-creatinin-diet.

Uric Acid.—The most marked difference between the figures for the partition in the two groups is found in the uric acid. The quantity of uric acid eliminated averages nearly twice as much on the creatinin-free as on the standard diet. It forms a little over 2 per cent. of the nitrogen as a rule on the creatinin-free diet, and about 1 per cent. on the standard diet.

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[7] Folin: Am. Jour. Physiol., 1905, **13,** 45 and 66.

SUMMARY

A study of the nitrogen partition in the urine of two groups of healthy children was made to establish normal figures. One group was fed on an ordinary or standard diet containing meat and vegetables, with the quantity regulated by age periods. The second on a creatin-creatinin-free diet in which the quantity of food (and hence of nitrogen) was regulated according to body weight. In both groups the N partition was practically the same, with the exception of the uric acid nitrogen. Urea N makes up from 80 to 85 per cent. and ammonia N from 3 to 5 per cent. The combined figure for the two is less than 90, rather than above 90, as in adults. Creatin is constantly present, as is creatinin. The two combined form a smaller percentage than the creatinin alone in the adult. The amount of undetermined or "rest" N is high in children.

GESTATION VERSUS STAGE OF LACTATION AS FACTORS CAUSING ABNORMAL COMPOSITION OF COW'S MILK*

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All regulations[1] standardizing cow's milk for human consumption exclude its use for a period of time before parturition, the period varying from fifteen to sixty days. Standards of this character are based on the supposition that pregnancy influences the normal composition of milk; in other words, that the milk no longer has a normal composition after gestation has reached a certain stage. The evidence on which this supposition is based is, however, extremely difficult to find, although the literature is extensive with regard to variations in the composition of milk.

The question of the factors influencing the normal composition of cow's milk has for several years been the object of critical study by the Missouri Agricultural Experiment Station. Certain portions of data, which were obtained for another purpose,[2] give a clearer insight into the importance of gestation as a factor causing milk of abnormal composition than any data yet published on this question. It is the purpose of this paper to present those data, together with some additional data, which have a bearing on the question of whether it is the stage of the gestation period or the stage of the lactation period which is the important factor causing milk of abnormal composition as the cow approaches parturition.

SOURCE AND CHARACTER OF DATA

The data presented represent the analyses of the milk and milk fat during the last days of the lactation period of twelve cows, representing four breeds, namely, Jersey, Holstein, Ayrshire and Shorthorn. The analyses for each sample of milk are more complete than any so far

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[1] For example, the standards adopted for "Certified Milk" by the American Association of Medical Milk Commissions (Proc. Sixth Ann. Conference, Am. Assn. Med. Milk Comm., 1912, p. 124) exclude the milk for a period of forty-five days before parturition.

[2] Eckles, C. H., and Shaw, R. H.: Influence of the Stage of Lactation on the Composition and Properties of Milk. U. S. Department of Agriculture, Bureau of Animal Industry, Bull. 155, January, 1913.

reported bearing on this question. All the cows were pure-bred dairy animals. All except one, Cow 22, received the same uniform ration for the entire lactation period from which the data are taken. The ration consisted of choice alfalfa hay and a grain mixture of corn 8 parts, bran 1 part and oats 1 part. Cow 22 was on pasture with additional grain at the time the data were taken. All the cows were pregnant with the exception of Cow 118. Complete analyses are reported for both the milk and milk fat. For the milk the data include the specific gravity and the percentage of total solids, fat, lactose, total protein and casein. The data in regard to the milk fat include the following physical and chemical constants: saponification value, Reichert-Meissl number, iodin-absorption value, and melting point. The methods of analyses used were those of the Association of Agricultural Chemists.[3]

DESCRIPTION OF TABLES

In Table 1 is presented the composition of the milk and milk fat for a seven-day composite at the close of the lactation period of each of the cows, in comparison with the true average composition for the entire lactation period. The latter values for each cow follow the letter (a), while the values for the seven-day composite at the last of the lactation period follow the letter (b). For several of the cows the last day of the seven-day composite was the last day of the lactation period. Some of the others were milked for a few days longer, this amounting to seventeen days in the case of Cows 300, 301 and 118. Two of the animals, namely, Cows 4 and 403, were milked for several weeks after the last sample was taken, Cow 4 being milked for four weeks, in fact up to the next parturition, and Cow 403 for five weeks. The data from the several cows are arranged in the order of the number of days before parturition when the last samples of milk and butter were taken for analysis. This varied in the different cows from thirteen to ninety-three days.

The figures following the letter (c) for certain of the animals are data similar to those following (b), the difference being that they represent a seven-day composite ending forty-five days before parturition. These data are given for purposes of comparison with the regulations of the American Association of Medical Milk Commissions.

Some additional data are given in the table, such as, (1) the stage of the lactation period when the samples were taken, (2) daily milk flow of each cow at the beginning of lactation and at the time the samples were taken, with the percentage drop, and (3) the length of time each cow was dry before the next parturition.

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[3] U. S. Department of Agriculture, Bureau of Chemistry, Bull. 107 (Revised), 1908.

TABLE 1.—RELATION OF STAGE OF LACTATION AND GESTATION TO THE COMPOSITION AND PROPERTIES OF MILK AND MILK FAT

			Milk Flow per Day				Composition of Milk							Composition of Milk Fat			
Cow	Time Before Parturition of Sample, Days	Stage of Laetation of Sample, Days	At First, Lbs.	At End, Lbs.	Drop, per Cent.	Time Dry, Days	Sp. Gr.	Total Solids, per Cent.	Lactose, per Cent.	Fat, per Cent.	Total Protein, per Cent.	Casein, per Cent.	Relation of Casein to Total P., per Cent.	Saponification Value	Reichert-Meissl No.	Iodin Value, Hübl	Melting Point, C.
209 (a)	.....	...	....	....	....	..	......	11.35	4.25	3.10	3.21	2.49	77.5	229.1	24.44	35.48	32.0
209 (b)	13–20	351	34.2	6.9	79.9	13	1.0344	13.43	4.52	4.01	4.60	3.64	79.1	215.8	20.93	39.06	37.8
209 (c)	45–52	319	34.2	10.6	71.1	..	1.0344	13.70	4.57	3.75	4.66	3.77	80.8	221.4	22.28	36.63	34.4
205 (a)	.....	...	....	....	....	..	......	12.12	5.05	3.23	3.00	2.49	83.0	228.2	25.81	34.46	33.8
205 (b)	19–26	394	26.3	4.8	81.7	12	1.0332	13.08	4.22	3.53	4.53	3.83	82.1	204.3	10.09	42.22	47.3
205 (c)	45–52	368	26.3	9.4	64.2	..	1.0330	13.54	5.10	3.61	3.96	3.51	88.7	200.1	7.63	44.96	52.9
22 (a)	.....	...	....	....	....	..	......	15.35	5.26	5.18	4.03	3.16	78.5	232.4	28.85	28.62	33.2
22 (b)	25–27	354	11.4	3.1	73.7	20	1.0357	16.11	4.50	5.35	5.30	4.08	77.0	211.4	12.05	41.53	31.9
22 (c)	45–52	334	11.4	9.3	18.4	..	1.0314	14.84	5.25	4.98	3.88	3.08	79.4	224.4	20.49	41.53	34.2
99 (a)	.....	...	....	....	....	..	......	13.34	4.95	4.64	3.27	2.65	81.0	228.6	28.69	28.87	33.0
99 (b)	25–32	334	23.6	4.5	80.9	21	1.0349	16.24	6.20	6.07	4.34	3.45	79.5	217.7	14.64	31.12	34.6
99 (c)	45–52	314	23.6	7.9	66.5	..	1.0323	14.85	4.78	5.42	3.89	3.19	82.0	224.0	23.60	30.45	35.0
4 (a)	.....	...	....	....	....	..	......	14.09	4.85	4.87	3.70	2.93	79.2	231.3	28.17	29.99	32.9
4 (b)	28–35	298	25.7	12.6	50.9	0	1.0340	14.80	4.42	5.68	4.27	3.38	79.0	227.6	25.87	32.18	33.0
4 (c)	45–52	282	25.7	11.4	55.6	..	1.0340	14.55	4.44	4.82	4.46	3.38	75.8	227.2	26.50	32.62	33.2
403 (a)	.....	...	....	....	....	..	......	12.17	4.98	3.37	3.28	2.62	79.8	227.9	26.29	34.72	32.9
403 (b)	53–60	312	30.3	4.1	86.5	19	......	13.31	4.40	4.10	4.08	3.13	76.7	224.9	23.03	35.88	33.3
300 (a)	.....	...	....	....	....	..	......	12.08	4.85	3.51	3.11	2.62	84.2	228.4	26.34	31.14	33.8
300 (b)	75–82	281	27.9	3.1	88.6	58	1.0340	14.14	3.74	4.65	4.60	3.90	84.8	216.7	17.43	39.64	33.3
402 (a)	.....	...	....	....	....	..	......	13.01	4.91	4.13	3.49	2.87	82.2	226.9	25.55	34.09	33.4
402 (b)	79–86	279	21.6	3.2	85.2	79	1.0314	13.37	4.14	4.50	4.53	4.15	91.6	210.4	14.98	41.33	37.1
400 (a)	.....	...	....	....	....	..	......	13.08	5.04	3.89	3.40	2.74	80.6	227.6	26.89	34.08	33.6
400 (b)	83–90	308	22.7	4.3	81.0	83	1.0303	12.79	4.29	4.20	3.70	3.45	93.3	216.5	22.41	38.77	36.6
206 (a)	.....	...	..	....	....	..	......	10.73	4.26	2.93	2.70	2.11	78.1	230.1	26.13	32.68	32.9
206 (b)	83–90	310	45.4	4.5	90.1	73	1.0346	13.95	4.48	3.73	4.91	3.89	92.8	215.4	15.27	37.62	35.2
301 (a)	.....	...	....	....	....	..	......	12.71	4.96	3.85	3.33	2.81	84.5	227.9	25.52	32.06	33.2
301 (b)	93–100	359	20.4	4.6	77.5	76	1.0375	13.02	4.90	4.48	4.41	3.83	87.1	219.5	18.58	36.35	33.7
118 (a)	.....	...	....	....	....	..	......	15.02	4.80	5.36	3.97	3.13	78.9	227.2	23.28	32.79	33.0
118 (b)	Farrow	394[1]	14.3	6.6	53.8	..[2]	1.0370	17.97	5.11	7.30	4.85	3.64	75.0	216.5	11.70	32.41	37.4

1. Cow in milk 411 days.

2. Cow not in milk again.

In Table 2 is shown the relation of the time before parturition to certain abnormalities in the composition of the milk and milk fat of each animal. The characteristics of the milk considered in this table are the percentage of total protein and fat, and the Reichert-Meissl number of the milk fat. The standards chosen as the limits of normality are 4.5 per cent. fat and 4 per cent. protein,[4] and a minimum Reichert-Meissl number of 24.00[5] for butter fat. The time given in the table is the number of days before parturition when the three characteristics passed beyond these limits of normality.

TABLE 2.—Relation of Time Before Parturition to Abnormal Milk

Cow	Protein, per Cent.	Time, Days	Fat, per Cent.	Time, Days	Reichert-Meissl Number	Time, Days
209	4.15	62	6.54	23	20.31	107
205	4.02	29	....[1]	...	21.83	99
99	4.08	55	....[2]	...	23.60	62
4	4.21	49	....[2]	...	.....[3]	...
403	4.08	60	....[1]	...	23.03	49
300	4.08	92	....[1]	...	23.25	113
402	4.08	110	4.71	110	22.38	145
400	....[4]	...	....[1]	...	23.33	128
206	4.15	107	....[1]	...	23.08	135
301	4.15	103	....[1]	...	22.26	110

1. Did not exceed 4.5 per cent.
2. Animal normally tested over 4.5 per cent.
3. Did not go lower than 24.00.
4. Did not exceed 4.0 per cent.

DISCUSSION OF DATA

An examination of Table 1 with the above standards in view shows at once that the stage of the gestation period bore no relation to the time the milk and milk fat passed the limits of normality chosen for comparison. Only a few specific citations are necessary to establish this fact. For example, both the milk and milk fat showed greater abnormalities in composition in the case of Cow 206 when she was three months from parturition than in the case of Cow 209 when she was only two weeks removed from parturition. Again, no greater abnormalities in composition of milk and milk fat are shown in the entire table than by Cow 118, which was farrow. Finally, the samples which show the least abnormality are those from Cows 4 and 403, particularly with respect to the composition of the milk fat. It was these animals whose milking period was continued the longest after the last sample was taken for analysis, this being four weeks in the case of Cow 4, and five weeks in the case of Cow 403. It is clear that when the last sample was taken for analysis in the case of these animals neither of them had reached a stage in their lactation period which corresponded with that of the other animals from which data are presented.

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[4] These are the standards for certified milk of the American Association of Medical Milk Commissions, adopted as those best suited for purposes of diet and nutrition.

[5] The minimum legal standard for butter fat of the United States Pure Food Laws.

An interesting feature of the table is the relation between the casein and total protein of the milk at the time the last sample was taken, in comparison with the relation which prevailed throughout the entire lactation period. The data show that in most cases the same relation existed at the close of lactation as throughout the lactation period, indicating that the protein increase in milk, which is characteristic of advancing lactation, is more or less of a concentration of protein constituents and not essentially an increase in the output of casein.

It is also clear from Table 1 that for seven of the twelve animals the milk passed the limits of normality chosen for comparison long before they had reached that stage of gestation, that is, forty-five days before parturition, which is most commonly recommended as that beyond which cows no longer give normal milk. The data in Table 1 following the letter (c) are accordingly given to see whether the forty-five day standard sufficed for the remaining five animals. An examination of these data shows that the milk of Cow 209 would have been excluded with fairness on account of the high protein content and the abnormal composition of the milk fat. The exclusion of the milk of Cows 205, 22 and 99 would not have been fair, however, on the basis of percentage of protein, which was in each case within the limits of normality chosen. An exclusion of the milk of these cows on the fat percentage basis would also have been unfair although the fat exceeded 4.5 per cent. in the case of Cows 22 and 99. These two animals were Jerseys, and their milk normally tested in excess of the 4.5 per cent. standard. It is worthy of note, however, that the milk fat of all three animals was abnormal in composition, particularly Cow 205. In the case of Cow 4 the exclusion of the milk at this time with fairness would also have been very questionable inasmuch as the milk was still following closely the average composition of the lactation period in all respects with the exception of a slightly increased total protein. It may be pointed out in connection with the data considered under (c) that each cow was still giving a gallon or more of milk a day. Dairy cows giving this quantity of milk are found in the herds of most dairymen, for it is the usual practice to continue the milking period as long as possible.

While considering the question of the standard of forty-five days before parturition, it is of interest to ascertain the length of time before parturition when the milk of the animals under discussion passed the limits of normal composition with which our data have been compared. This point is considered for certain of the animals in Table 2. The wide variation between the individual animals, and also from the forty-five day standard, is very striking.

DISCUSSION OF RESULTS

It is important to state that the data and discussion presented in this paper are not offered in any sense in criticism of the standards of normality with which the data have been compared. These standards have been used for comparison because they were adopted with the problem of infant feeding especially in view, and because we believe our data have particular bearing on that problem. We believe, however, that the standards might well be extended to include the composition of the milk fat as indicated by some one or more of the chemical or physical constants. Unfortunately, no information is at present available in regard to the relation of the composition of the fat of cow's milk to its suitability as food for infants, or as a matter of fact, for human food in general. It is clear, however, to any one who studies the question with an open mind, that it is easy for the dietitian to remedy an abnormal percentage of the milk constituents by the usual methods of modifying milk for infant feeding. An abnormal composition of the milk fat, however, cannot be corrected by these means.

The question on which our data have particular bearing is whether any milk standards are justified in excluding milk for use on the basis of the stage of the gestation period. Our data seem to us to show clearly that this is not the correct basis. The abnormalities to which cow's milk is subject when parturition is approaching are due largely, if not entirely, to the stage of the lactation period. The data here presented indicate clearly that cow's milk becomes abnormal in composition as soon as the lactation stimulus becomes an artificial one on the part of the dairyman, and that this result bears no relation to the stage of the gestation period. Many cows show these abnormalities several months before the next parturition, while very heavy producing cows with periods of parturition the usual interval of twelve to thirteen months apart, may continue to produce perfectly normal milk up to the very hour of the next parturition. The latter are the exception, however, rather than the rule. The great majority of dairy cows in this country are relatively small producers. In these cases the high protein and fat content, and abnormal composition of the milk fat characteristic of the end of the lactation period may become important questions in connection with infant feeding long before the forty-five day limit is reached. Where mixed milk of a large herd is used the danger of wide variations due to the end of the lactation period would naturally be less likely to occur. The great danger lies in the small herd of cows which are likely to freshen about the same time of the year, and especially in the case of the family cow, in both of which cases the common practice is to continue milking the animals as long as possible.

To those who may desire to make use of the facts here presented, one very practical question arises in this connection, namely, what criterion is available by which the end of the lactation period can be judged? The percentage decrease in the milk flow from that when the cow was fresh is some indication of the stage of the lactation period. This information was given in connection with the data in Table 1 with this point in view. The relations are not definite enough, however, for the establishment of any safe rule that can be followed. Moreover, this information would usually be difficult to secure with accuracy. The milk from cows giving as low as a half-gallon a day should certainly be regarded with suspicion, and should be subjected to critical analysis, especially where the feeding of infants and children is concerned.

Dairy Building.

THE BACTERIOLOGY OF THE URINE IN CHILDREN WITH VULVOVAGINITIS

WITH A REPORT OF TWO CASES OF GONOCOCCUS CYSTITIS *

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The conception of an ascending route of infection in cystitis of infancy has heretofore largely rested on the unproved assumption of a constantly contaminated urethral tract. Such a hypothesis served to explain the predominance of cystitis in female infants. Helmholz and Beeler[1] in a recent study of the bacteriology of the urine in normal children, and of the urine from children with extra-urinary infections, established conclusively that the organisms of the colon group are not normal inhabitants of the female urethra. They further demonstrated that in those instances of extra-urinary infection in which organisms were found in the urine, these were present in such small numbers that they could not be considered other than accidental contaminations from the urethra.

If the incidence of cystitis were subject to local factors, then any condition which increased such local factors should militate against a sterile urinary tract. It therefore seemed important to study the bacteriology of the urine in children with vulvovaginitis. For we have in this disease inflammatory changes the contiguity of which to the urethra might conceivably produce a *locus minoris resistentiae,* which would favor contamination of the urinary tract with resulting cystitis. The bacteriology of the urine from eighteen unselected patients with chronic gonococcus vulvovaginitis was studied. These patients were all over 2 years of age. Catheterized specimens were obtained and cultures made, using the technic and method described by Helmholz and Beeler.

Two specimens were obtained from each patient, the first representing approximately the flora of the urethra, the second that of the bladder. A portion of the first specimen was examined for albumin, another part centrifuged and examined in stained smears for bacteria and unstained for cellular elements.

At the time of catheterization, thirteen of these eighteen patients presented more or less vaginal discharge, and all of the eighteen had leukocytes in their vaginal smears. Only five showed gonococci in the vaginal smears at the time of catheterization. None of these eighteen

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[1] Beeler, C., and Helmholz, H. F.: Bacteriology of the Urine in Healthy Children Suffering from Extra-Urinary Infections, AM. JOUR. DIS. CHILD., 1916, **12,** 345.

TABLE 1.—BACTERIOLOGY OF THE URINE IN CASES OF VULVOVAGINITIS

Case No.	Vulvovaginal Findings			Urine Examination		Cultures of Specimen 1		Cultures of Specimen 2		Remarks
	Discharge	Leukocytes	Gonococci	Albumin	Microscopic	Colonies per C.c.	Types of Organisms	Colonies per C.c.	Types of Organisms	
1	+	+	+	—	Negative	10	Staphylococcus albus; diphtheroid bacillus	Less than 1	Gram + coccus	Diphtheroid bacillus, which constituted majority of colonies, appeared only on a blood agar plate
2	+	+	—	—	Negative	0	....	0	....	
3	+	+	—	—	Stained sediment shows large gram + coccus	Innumerable	Staphylococcus albus	Innumerable	Staphylococcus albus	Identical findings on recatheterization 18 days later
4	+	+	+	—	Negative	0	....	Less than 1	Bacillus subtillis	Only 1 colony present, this not appearing until 6th day on blood agar plate
5	—	+	—	Faintest trace	Negative	Less than 1	Bacillus subtillis	0	....	Only 1 colony present, this on the blood agar plate
6	—	+	—	—	Negative	3	Staphylococcus albus	10	Staphylococcus albus	Specimen 2 inoculated in deep dextrose blood agar tube only
7	+	+	—		Negative	Less than 1	Diphtheroid bacillus; gram + coccus	Less than 1	Diphtheroid bacillus	
8	+	+	—	—	Negative	3	Staphylococcus albus; gram + diplococci	2	Gram + coccus; gram + diplobacillus	
9	+	+	+	—	Negative	Less than 1	Bacillus subtillis	1	Staphylococcus albus; gram + diplococcus	
10	+	+	—	—	Negative	0	....	0	....	
11	—	+	—	—	Negative	6	Gram + diplococcus	6	Gram + diplococcus	
12	—	+	—	—	Negative	1	Gram + diplobacillus; Staphylococcus aureus; diphtheroid bacillus	10	Gram + diplococcus	Only medium showing growth from Specimen 2 was deep tube of dextrose blood agar
13	+	+	—	—	Stained sediment shows gram — coccus. No cellular elements	0	....	0	....	
14	—	+	—	—	Negative	3	Diphtheroid bacillus; gram + diplobacillus	0	....	
15	+	+	—	—	Negative	2	Diphtheroid bacillus; gram + diplococcus	0	....	
16	+	+	—	—	Negative	0	....	0	....	Only Specimen 2 cultured
17	+	+	+	+	Large number of pus cells; stained sediment shows leukocytes with gram — diplococci	Less than 1	Staphylococcus albus	Less than 1	Gram + diplobacillus	Urine milky; contains flocculi; acid reaction
18	+	+	—	+	Large number of pus cells; stained sediment shows leukocytes with gram — diplococci	Less than 1	Gram — short diplobacillus; would not grow in subcultures	0	....	Urine milky; contains flocculi; acid reaction

patients, however, had had vaginal smears negative for gonococci for any three consecutive weeks (a requirement prior to discharge of such patients from this hospital).

The bacteriologic findings were as follows: (Table 1) Specimen 1 was sterile in five instances, in ten instances gave less than 3 colonies per cubic centimeter, in one instance 6 colonies per cubic centimeter, in one instance 10 colonies per cubic centimeter, and one showed innumerable colonies. Specimen 2 was sterile in eight instances, gave 1 or an average of less than 1 colony per cubic centimeter in five instances, 2 colonies per cubic centimeter in one instance, 6 colonies per cubic centimeter in one instance, 10 colonies per cubic centimeter in two instances, and one showed innumerable colonies. From the same patient whose urine gave a profuse growth of a *Staphylococcus albus* in both Specimens 1 and 2, subsequent catheterization and cultures brought identical findings. This urine showed no other abnormalities, nor did the particular patient exhibit any subjective evidence of urinary disturbance.

TABLE 2.—Bacteriology of the Urine After Recatheterization

Case No.	Vulvovaginal Findings			Urine Examinations		Cultures	
	Discharge	Leukocytes	Gonococci	Albumin	Microscopic	Colonies per C.c.	Types of Organisms
1	—	+	+	—	Negative..........	2	Diphtheroid bacillus
2	—	+	—	—	Negative..........	2	Staphylococcus albus
3	+	+	—	—	Negative for cellular elements	Innumerable	Staphylococcus albus
4	+	+	+	—	Negative..........	0	
5	—	—	—	—	Negative..........	Less than 1	Diphtheroid bacillus
6	—	+	+	—	Negative..........	0	
7	—	+	—	—	Negative..........	0	
8	—	+	—	—	Negative..........	1	Staphylococcus
9	—	+	—	—	Negative..........	Less than 1	Gram negative bacillus
10	+	+	—	—	Negative..........	Less than 1	Bacillus, gram ±

The character of the organisms obtained were very similar to those reported in the series of normals by Helmholz and Beeler, namely, gram-positive cocci and diphtheroid bacilli. In no instance was a gram-negative bacillus encountered.

In Cases 17 and 18, however, as shown in Table 1, the sediment, even uncentrifuged, showed masses of pus cells, with occasional leukocytes filled with gram-negative, biscuit-shaped diplococci. These two instances will be discussed at greater length in the latter part of this article.

After an interval of several weeks, ten of the patients, who were kept constantly under observation in the interval, were again catheterized, slightly varying the methods of study. In the series of recatheterizations (Table 2; the numbers correspond with case numbers in Table 1) Specimen 1 was used for centrifugation and microscopic study but was not cultured. Specimen 2 was planted on plates of lactose litmus agar and ascites dextrose agar, the former to make identification of any of the colon group easier, the latter for growth of the gonococcus. The total result, practically negative findings in the series of recatheterizations, is a circumstance of striking importance. It is noted that in not a single instance, as shown either by the clinical urinary analysis or by the bacteriologic findings, does the recatheterization reveal any urinary infection which might be conceived as following either the vulvovaginal infection or the first catheterization per se. In only one instance, the patient with staphylococcus bacteriuria mentioned previously, were the bacteria present in such numbers that they could not be considered as accidental contamination from the urethra. Of the ten specimens, three were sterile, all the others but one showing less than 2 colonies per cubic centimeter. The few organisms encountered were either staphylococci or diphtheroid bacilli, except in Case 9, in which the ascitic dextrose agar plate showed one colony, a gram-negative bacillus.

Comparing the results of the present series with those reported by Helmholz and Beeler in children over 2 years of age, a difference is only noted in regard to Specimen 1. Of their series, 83 per cent. showed 1 colony or less per cubic centimeter. In the present series this percentage is 58, giving a smaller number of practically sterile urines in those obtained from patients with vulvovaginitis. In the comparison of the results obtained from cultures of Specimen 2, this difference disappears. Of their series, 73 per cent. showed either a sterile urine or less than 1 colony per cubic centimeter. In the present series 72 per cent. showed the same findings. The negligible difference in results with Specimen 1, is easily explained, in that it is quite conceivable that during a vulvovaginitis, the distal end of the urethra may harbor more bacteria than normally, and Specimen 1 of these respective series represents this flora as well as that of the deep urethra. Specimen 2, however, representing the bladder flora, shows the same comparative absence of organisms in the urine of patients with vulvovaginitis as was demonstrated in that obtained from normal children.

GONOCOCCUS CYSTITIS

Notwithstanding the frequency of gonococcus vulvovaginitis in childhood, particularly as met with in hospital practice, and the numerous reports that have been published regarding this disease, one is struck with the very meager data at hand regarding gonococcus cystitis in childhood. Statistical tables in the majority of investigations are conspicuously silent on this complication, many not mentioning it, others noting a rare case with few details in a large series of observations. Welt-Kakels[2] notes that gonococcus cystitis is but very rarely observed, having seen only one case in a series of 190 children with vulvovaginitis. Edith Spaulding,[3] reporting 5 cases of cystitis among 74 children with vulvovaginitis, says: "We believe cystitis is much more common than is realized, but as the urine is not examined in every case, it is often not discovered." Neither of these observers states how the diagnoses were reached in their cases. It should be remarked that even with urinalyses, cystitis may be overlooked, the cellular elements encountered being attributed to the vaginal discharge rather to coexistent cystitis. This is probably the most frequent source of error and may account for the infrequency of hospital diagnoses of this condition. In this connection it might also be stated that presence of leukocytes in a vaginal smear, sometimes wrongly interpreted as evidence of a latent vaginitis, may occasionally be due to an undiagnosed cystitis of *Bacillus coli* origin.

In the present series of vulvovaginitis cases two instances of gonococcus cystitis were encountered. It is extremely interesting that both of these patients had had previous infection of the urinary tract, one having entered the hospital with a colon cystitis, the other with a mild nephritis associated with a colon bacilluria, vulvovaginitis developing in both at a later time. Their persistent cystitis had not aroused any suspicion of the true infection until they were catheterized for the purpose of the previous study. Like many other patients with cystitis, there were no subjective complaints. On this catheterization and on later catheterization, the urine obtained in both instances was of a milky character and held suspended numerous fine flocculi. Uncentrifuged smears showed innumerable pus cells, many exhibiting the characteristic inclusion of gram-negative diplococci. It is of course impossible to state when the *Bacillus coli* had been displaced by the gonococcus as the infecting organism. One of these patients was cystoscoped by Dr. Herman L. Kretschmer. The bladder showed a cystitis at the trigonum, the usual pathologic picture of such infections. The ureteral orifices as seen with the plain cystoscope appeared normal.

These instances afford another possible explanation for the occasional protracted case of vulvovaginitis that is refractory to treatment. Such a bladder mucosa might act as a source of reinfection of the vaginal tract.

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[2] Welt-Kakels: New York Med. Jour., 1904, **80**, 780.

[3] Spaulding, E. R.: Vulvovaginitis in Children, Am. Jour. Dis. Child., 1913, **5**, 248.

The difficulty of cultivation of these organisms from the urine has been noted by Colombini[4] and others. Whether this same slow growth of the gonococcus accounts for the apparent rarity of this organism as a cause of cystitis in children, may only be conjectured. It has been shown by several investigators that the mere presence of the gonococcus in the bladder will not produce a cystitis.[4] In these particular instances the previous infection by the *Bacillus coli* may have produced changes in the bladder mucosa favorable for subsequent infection by the gonococcus.

SUMMARY

In eighteen unselected patients with chronic gonococcus vulvovaginitis, carefully catheterized specimens of urine showed a comparative absence of bacteria. The majority of the organisms encountered were either gram-positive cocci or diphtheroid bacilli. In most instances these were in such small numbers that they could easily be accidental contaminations from the urethra.

The second portion of the urine, representing the bladder flora, was shown to be as free from infecting organisms as was demonstrated in a previous series of normals. The occurrence of vulvovaginitis did not increase the tendency to contamination of the bladder.

Gonococcus cystitis may follow previous infections of the bladder by *Bacillus coli* in patients with vulvovaginitis.

410 Goldsmith Building.

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[4] Colombini: Quoted by Young, H. H.: Johns Hopkins Hospital Rep., 1900, **9**, 677.

CLINICAL DEPARTMENT

REPORT OF A CASE OF CONGENITAL ENDOCARDITIS

WITH ACUTE VEGETATIVE INFLAMMATION OF THE PULMONARY ARTERY AND VALVE *

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On reviewing the literature pertaining to this subject one is impressed by the infrequency of the condition, and by the large percentage of the cases coming to necropsy undiagnosed.

Hirschfelder[1] reports only three cases of 24,000 medical admissions to the Johns Hopkins Hospital, and of this number only one case was diagnosed during life.

In Abraham's[2] clinic in the New York Post Graduate Hospital, in which nearly 800 cases are studied yearly, only one case of pulmonary insufficiency has been encountered in the past eleven years.

Willigk,[3] in 4,547 dead bodies, found inflammation of the pulmonary valves nine times; twice this valve alone was involved.

Berthram Abraham[4] found, in 300 necropsies held on subjects of heart disease at Westminster Hospital, that thirty-nine showed ulcerative valvular changes. In only one were the pulmonary valves involved, and this involvement was associated with aortic and tricuspid ulceration. Out of 16,000 postmortem examinations at Guy's Hospital[5] only twenty-four showed pulmonary incompetency.

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* Submitted for publication Dec. 22, 1916.

* Read before the Medico-Chirurgical Society, Dec. 8, 1916.

[1] Hirschfelder: Diseases of Heart and Aorta, Philadelphia, 1913, p. 480.

[2] Abraham, R.: A Case of Pulmonary Insufficiency, Jour. Am. Med. Assn., 1913, **60,** 1150.

[3] Willigk: Quoted from Allyn, Insufficiency of Pulmonary Valves, Am. Jour. Med. Sc., 1913, **146,** 541.

[4] Abraham, B.: Brit. Med. Jour., 1899, **2,** 1273.

Babcock[5] has encountered in his observation of heart conditions only one case of acute pulmonary endocarditis; even in this one a postmortem was not obtained.

In 846 Munich cases the pulmonary valves in general were involved in 1.54 per cent.; alone in 0.59 per cent.

In Parrot's[6] 1,058 cases of valvular involvement, only 0.01 per cent. showed the pulmonary valve to be affected. On the other hand, Sperling[7] is credited with saying that in 4 per cent. of combined valvular lesions the pulmonary valves are involved in a greater or less degree.

The clinical terms, pulmonary insufficiency, regurgitation, and incompetency, etc., which the above statistics embrace, are commonly used to signify any condition referable to the pulmonary valve. These general terms, as we shall see later, lead one astray, when the true nature of the condition is ascertained. They mean nothing to the internist from the prognostic point of view. To the pathologist they furnish no light as to the etiology of the condition, nor do they convey to the anatomist a congenital deformity, which is so often encountered and referred to in these terms.

Thus, for the sake of clearness, we will classify pulmonary valve conditions into (1) congenital and (2) acquired.

Congenital.—Under the general heading congenital, we have (1) structural changes; namely, maldevelopment, irregularity in form of the valves; (2) organic changes, or fetal endocarditis. Acute fetal endocarditis has never been encountered as far as we have been able to ascertain from the literature. The common form is the sclerotic type, that is to say, the valves are thickened and contracted and the edges often united to those adjoining. The warty variety does occur, but is of far less frequency.

The etiology of fetal endocarditis is not definitely known, but it is thought by some, though hypothetically, that rheumatic fever during pregnancy, or a tendency of the mother to rheumatic attacks, is a cause. Suffice it to say, it is necessarily of chronic origin, as is shown by the diffuseness with which the valves are involved, and by the negative findings of acute manifestations.

We would therefore expect no other etiologic process than a mild, diffusible circulating toxin, filtering through the placental tissue and producing its results by constantly bathing the valves. If this be true, then all the valves of the heart would be more or less affected; however, it is conceded that an anomaly of the heart predisposes the site to attack, and as the right side of the heart is usually the seat of malformation in the fetus, it is natural that the right side of the heart should show the highest percentage of involvement. Rauchfuss[8] is credited with saying that the two sides of the heart are equally affected in fecal endocarditis, unless the heart is associated with malformation, in which case the endocarditis is more prominent on the right side.

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[5] Allbutt's System of Medicine, New York and London, 1906, **6**, 3.

[6] Osler and McCrae's Modern Medicine, 1915, **4**, 213.

[7] Satterthwaite's Diseases of the Heart and Aorta, New York, 1905, p. 31.

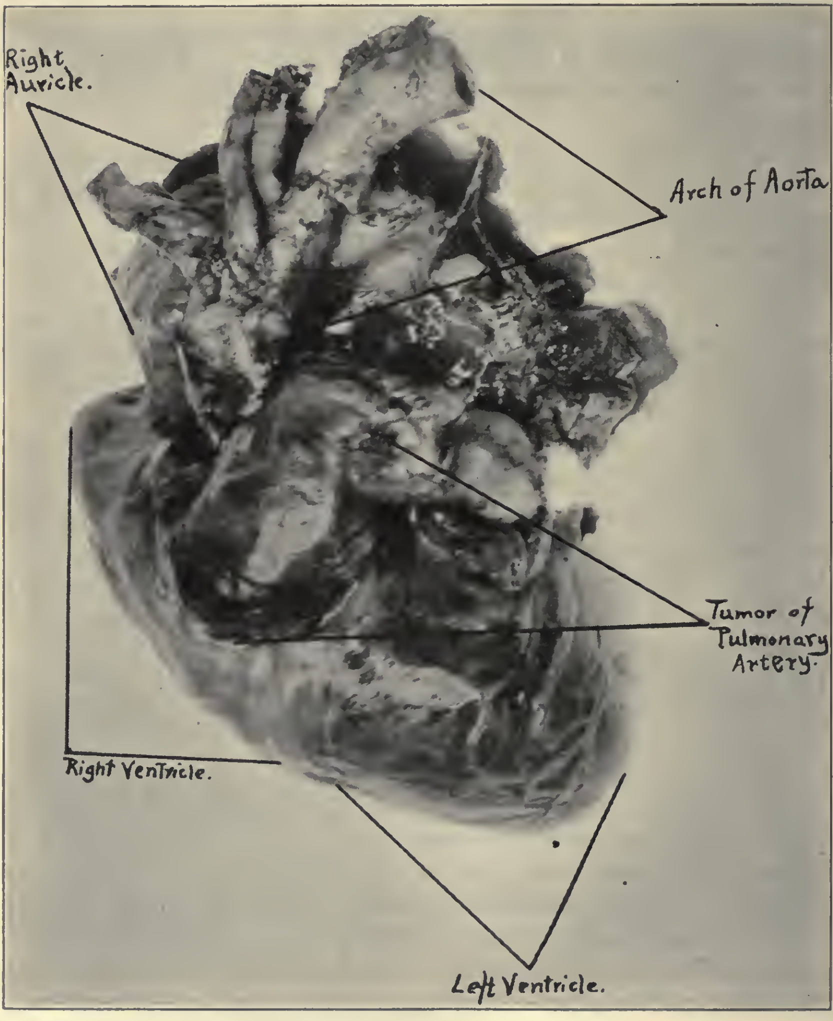

Fig. 1.—Showing the markedly enlarged pulmonary artery (from its origin to its bifurcation).

Acquired Varieties.—Organic Changes:

1. *Acute Infectious Valvulitis.*—This embraces the terms simple, vegetative and ulcerative endocarditis of the valves. There is no

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[8] Allbutt's System of Medicine, New York and London, 1906, **6,** 5.

definite distinction between these terms. The pathologic process is only one of degree. The etiologic agent, as cultured from the blood, in most instances will reveal the nature of the pathologic picture. That is to say, an endocarditis of pneumococcic or of gonococcic origin has a marked tendency to produce the so-called malignant or ulcerative type of endocarditis.

Acute infectious valvulitis is, according to Pitt,[9] the most frequent cause of pulmonary incompetency. Of the 109 cases of pulmonary incompetency collected from the literature and from Guy's Hospital records by Pitt, 60 cases were of this origin. In 19 of the 51 cases collected from Guy's Hospital reports, lesions of the other valves were associated. That fetal derangement is a factor in subjecting the pulmonary valve to postnatal infection is shown by Pitt's 60 cases of infectious pulmonary valvulitis, in which 21 occurred in a malformed heart, and 8 of the latter were of congenital pulmonary stenotic type.

It may be of interest to show the relative frequency of acute pulmonary valve involvement to other acute valvular conditions, which are summed up in the following statistics: Horder[10] collected from St. Bartholomew's Hospital 115 cases of ulcerative valvulitis; only seven times were the pulmonary valves involved, and then not alone, but each time with the mitral. At the Philadelphia General Hospital,[11] in 8,640 necropsies, 335 showed acute endocarditis; in these the aortic valve was involved 164 times, mitral 143, tricuspid 15, and pulmonary 7. In a review of 1,300 necropsies at the Pennsylvania Hospital,[11] 107 cases of acute endocarditis were found. Valvular involvement was as follows: aortic 25, mitral 47, both 23, aortic, mitral and tricuspid 2, mitral and tricuspid 4, tricuspid 3, pulmonary 1.

Washbourn[12] collected 309 cases of infective endocarditis. As to frequency of attack, the right side was involved alone in 13 cases, mitral alone in 116 cases, aortic alone in 69, aortic and mitral in 73, tricuspid in 28 and pulmonary in 19.

Unfortunately the majority of available statistics which deal with the occurrence of recent endocarditis give no information regarding the microscopic or bacteriologic examination. Among the etiologic agents that are reported in this condition, however, the gonococcus and pneumococcus head the list. In the 60 cases of pulmonary valve involvement reported by Pitt[9] 19 were produced by known organisms. Of the 19 cases, 8 were produced by the gonococcus and 5 by the pneumococcus.

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[9] Allbutt: System of Medicine, New York and London, 1906, **6**, 3.

[10] Horder: Quart. Jour. Med., 1908, **2**, 289 and 324.

[11] Norris: Studies in Cardiac Pathology, Philadelphia and London, 1911, p. 26.

[12] Washbourn, J. W.: Brit. Med. Jour., 1899, **2**, 1270.

Külbs'[13] analysis of 49 well authenticated cases of gonococcic endocarditis gives the following frequency of valves attacked: aortic 28 times; mitral, 8; pulmonary, 6; tricuspid, 1; aortic and mitral, 3; mitral and tricuspid, 1; all the valves, 1; all except pulmonary, 1.

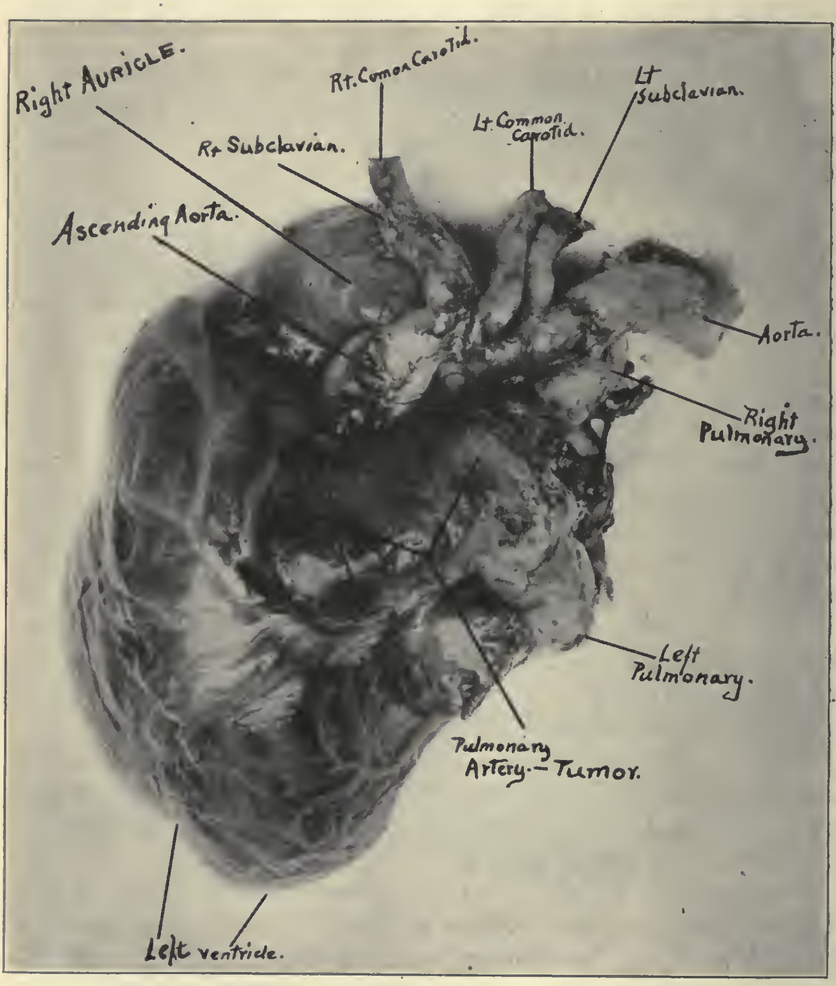

Fig. 2.—Showing the much enlarged right auricle, extending well above the arch of the aorta.

The only case of acute pulmonary endocarditis that was found in the Pennsylvania Hospital records, was of gonococcic origin.

Preble[14] reported five cases of pulmonary endocarditis caused by the pneumococcus.

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[13] Külbs: Wien. klin. Wchnschr., 1907, **20**, 11. Referred to by Irons, Arch. Int. Med., 1909, **4**, 601.

[14] Norris: Studies in Cardiac Pathology, Philadelphia and London, 1911, p. 20.

Callender[15] reported a case of pulmonary valve involvement alone, in which cultures made from the vegetation showed micrococcus endocarditis rugatus.

In valvular involvements other than the pulmonary, the streptococci, the pneumococcus, *Staphylococcus aureus,* colon bacillus, and influenza bacillus in the order named are among the more common etiologic agents. In forty cases reported by Horder,[16] 65 per cent. were of streptococcic origin. In 2,722 pneumonia cases collected by Norris,[17] acute endocarditis was found 158 times. Norris says that the aortic and pulmonary valves are involved more frequently in pneumonia than the other valves, but he does not tabulate their relative frequentcy.

The age distribution in acute pulmonary valve involvement in 49 cases reported by Pitt[3] is as follows: birth to 10 years, 2 cases; 11 to 20 years, 12 cases; 21 to 30 years, 15 cases; 31 to 40 years, 11 cases; 41 to 50 years, 4 cases; 51 to 60 years, 4 cases; 61 to 70 years, 1 case. In comparison with acute valvular lesions in general, Horder[18] found in 150 cases the greatest number between 20 and 30, namely 39; next between 30 and 40, 31; and between 15 and 20, 29 cases. From the statistics, therefore, the most frequent period of involvement of the pulmonary, as well as the remaining valves, is between the ages of 20 and 30.

2. *Chronic Valvular Endocarditis or Sclerosed Valves.*—This condition may be the result of repeated acute attacks, or chronic from the onset, as in the case of arteriosclerosis in general. What is true of other valves is apparently true, in the main, of the pulmonary valves. That is to say, types of sclerosis, from a pathologic standpoint, are much more common, according to the report made by Norris, than the acute variety. Among 8,640 necropsies at Blockley, the pulmonary valves were found sclerosed in forty-four cases, against seven cases that were found to be acutely attacked; whereas Pitt reports, as already noted, that incompetency of the pulmonary orifice is produced more frequently by acute inflammation than any other type of lesion. This apparent discrepancy in the report of necropsy findings is no doubt due to the general use of the term incompetency.

The contrast is more striking in valves other than the pulmonary, as is shown by the figures quoted from Hirschfelder,[19] namely, that only forty-five cases of ulcerative endocarditis occurred among 23,200 admissions as compared with 1,781 of the chronic valvular type.

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[15] Callender, S. P.: Am. Jour. Med. Sc., 1915, **149,** 723.

[16] Horder: Treatment with Vaccines, Practitioner, 1908, p. 714.

[17] Norris: Studies in Cardiac Pathology, Philadelphia and London, 1911, p. 18.

[18] Norris: Studies in Cardiac Pathology, Philadelphia and London, 1911, p. 16.

[19] Hirschfelder: Diseases of Heart and Aorta, New York, 1913, p. 392.

Sclerosed valves from any cause are more liable than healthy valves to be attacked by infective endocarditis. This is also true of valves in general, as is shown by the following statistics:[12] One hundred and fifty-seven of Osler's 209 cases, 61 of Goodhart's 69 cases, and 59 of Guy's Hospital 100 cases, and 64 of Norris' 107 cases were noted as having old valvulaar disease.

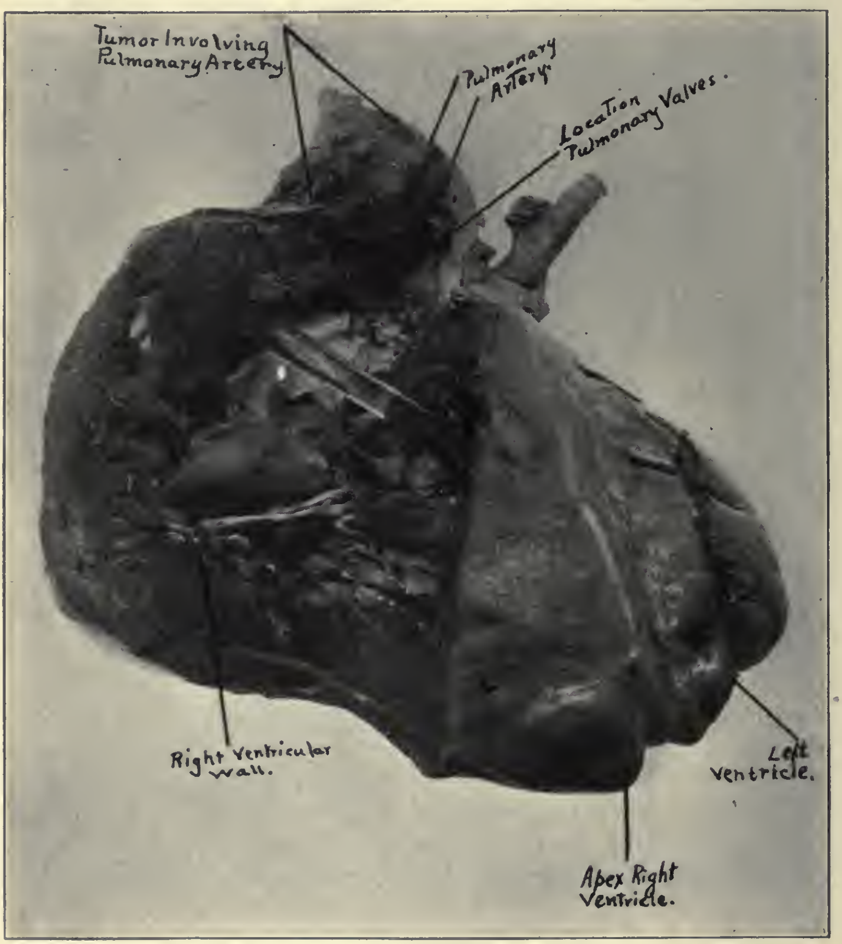

Fig. 3.—Showing the extensive vegetative inflammation of the pulmonary valves and anterior wall of the pulmonary artery, the thickness of the right ventricular wall and the prominence of the apex of the right ventricle.

Relative or functional dilatation of the pulmonary orifice is apart from the purpose of this communication and is therefore omitted.

With the foregoing references to the literature on unusual pulmonary conditions from an etiologic, anatomic and pathologic point of view as a preface, the following case is presented.

REPORT OF CASE

History.—J. H., a boy, aged 13, was admitted to the Orphans' Home, February, 1912, with a certificate from the examining physician to the effect that he was entirely normal in every respect.

The boy's father died in May, 1912, and mother in April, 1913, of tuberculosis. There were six children in the family; three are living and well, and three dead from tuberculosis. No history of any previous illnesses could be obtained either from the family physician or from those connected with him. After admission into the Home, however, the boy was found to be affected with trachoma and hookworm.

Examination on Admission.—On admission, at 9 years of age, physical examination showed him to be of a pasty appearance, undersize and underweight. He was far below the average in intelligence. His facial expression was motionless and mildly hideous. There were a bulging of both eyes, a congenital ptosis of the upper eyelids, bifurcated uvula, and two lower central incisor teeth of the typical Hutchinson type, while the upper central incisors were absent. The entire musculature of the body was undeveloped. There was clubbing of the fingers. The chest showed a prominent cone-shaped bulging of the sternum together with the costal arch on either side, the summit of which was located about the right third costosternal articulation.

A distinct systolic heaving and diastolic retraction of the intercostal spaces were noticed throughout the precordial area, being more pronounced in the second and third interspaces some distance to the left of the sternum. A slight pulsating mass was evident in the neck, situated behind the suprasternal notch. On palpation, a thrill, systolic in time, could be felt throughout the precordial area, being more pronounced in the first, second and third interspaces, just to left of sternum. With the finger tip, a perceptible thrill could be felt over the pulsating mass in the neck.

Percussion revealed an enlargement of the heart to the right of the sternum, and the apex in the nipple line. On auscultation a loud, blowing systolic, and a relative weaker diastolic, murmur were heard over the entire chest anteriorly, being more intense over the second space just to left of the sternum, and slightly diminished along the left border of the sternum to the apex of the heart. A distinct systolic bruit and a low blowing diastolic murmur were heard over the pulsating mass behind the suprasternal notch. There were no murmurs transmitted into the vessels of the neck. Radial and carotid pulses were equal in force and rhythm on both sides. The radial pulse was of good volume. A roentgenogram taken at this time by Dr. E. T. Bruce revealed a shadow to the right and above the outline of the heart.

Subsequent Course.—For the three years following his admission there was little development, either mentally or physically. He was able to play with his associates, but would become dyspneic on the least exertion. The pulsating mass behind the suprasternal notch grew larger and the precordial bulging became progressively greater.

June 11, 1916, the patient showed drowsiness and loss of appetite. The following day he developed a troublesome cough, together with bleeding of the nose and vomiting. The temperature was irregular until two days later, when it rose to 103 F., fluctuating between 100 and 103 F. for the ensuing three weeks; pulse ranged between 90 and 110; respirations between 30 and 40. On the fourth day of the illness there developed a consolidation of the left apex. Over this area fremitus was increased and the breath sounds were bronchial in type.

The blood count showed a leukocytosis; blood culture showed the pneumococcus. The Wassermann was negative.

A tracing made from the radial artery by Dr. Zahner two weeks after the initial onset showed an alternating pulse, which was interpreted by Dr. Greiwe to be of fatal omen. The tracing showed nothing else of interest.

On the twenty-fourth day of the illness, the temperature dropped to normal, but rose on the following day to 101 F., and fluctuated daily in this manner until death, which occurred six weeks after the initial onset. After the first drop in temperature, the original apical consolidation cleared up somewhat, but there remained a distinct impairment of resonance. During the fifth week of illness, distinct cavernous breathing was elicited over the right apex. The heart murmurs, as far as we were able to judge, remained constant both as to intensity and time. The same can be said of the murmurs in the pulsating mass behind the suprasternal notch.

Necropsy.[20]—Necropsy conducted seven hours postmortem. The body is that of a poorly developed, emaciated, white adolescent; edema absent. The marked bulging of the chest anteriorly and clubbing of fingers and toes have already been described.

Heart: Weight 350 gm. The right auricle is markedly enlarged, extending behind and well above the arch of the aorta. Its cavity is much distended with soft, dark-red, postmortem blood clots, and the wall measures 2 mm. in its greatest thickness. The foramen ovale is patent, funnel-shaped, the apex leading into the left auricle, and measures 5 mm. in diameter. The right ventricle shows marked hypertrophy, being larger than the left ventricle, as is shown by the following measurements:

	Right, Cm.	Left, Cm.
Longitudinal	8	10
Transverse	7	3
Anteroposterior	8	6

The right ventricle has a separate apex which extends 1 cm. below the apex of the left ventricle. There is a slight transverse finger-like depression along its anterior surface, 4 cm. below the atrioventricular septum. Its wall measures 7 mm. in thickness. The tricuspid orifice is somewhat dilated, measuring 9.6 cm. in circumference. Its valves are diffusely thickened and present on their auricular surfaces, 5 mm. from their free margins, three firm, pyramidal, pearly-white masses, the largest measuring 3 mm. at its base and 5 mm. from base to apex.

The pulmonary artery is much enlarged, measuring 3 cm. in diameter. Its anterior wall is firm and bulging, whereas its posterior wall is soft and flabby. The pulmonary orifice is almost entirely obliterated, permitting only the passage of a small probe. On opening the orifice and artery the valves are found to be covered with numerous small, very friable, pendulous vegetations which entirely obliterate the sinuses behind the cusps. Beginning with the valves and extending along the inner, anterior surface of the pulmonary artery for an area 2 by 3 cm., is a friable, moderately firm, grayish-brown, pedunculated, wart-like outgrowth. This outgrowth fills the lumen of the pulmonary artery from valves to bifurcation, except for a small canalicular passage along the posterior wall. Section throughout the mass reveals a surface grayish-white and semitranslucent, mottled with small grayish-yellow areas of pultaceous material.

The left auricle is apparently of normal size. The left ventricular wall is firmly contracted, being beefy-red in color, and measuring 8 mm. in thickness. The mitral valves are diffusely thickened and present pyramidal masses similar to those on the tricuspid valves. The mitral orifice measures 8 cm. in circumference. The aortic valves show a moderate amount of diffuse thickening, with slight intervalvular adhesions. The aortic orifice measures 4 cm. in circumference.

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[20] The necropsy was conducted by the Pathological Staff of the University of Louisville Medical Department.

Lungs: Dense, firm, fibrous adhesions anchor both organs to the chest walls. The right lung shows a cavity 2 by 1 cm., 2 cm. below the apex, containing grayish-yellow caseous material. Otherwise the lungs show nothing more than chronic passive congestion. Spleen: This is enlarged, measuring 17 by 9 by 4 cm.

Liver: This is firm, with edges somewhat rounded, surface brownish-yellow and finely nodular; cuts with increased resistance, cut surface presenting so-called nutmeg appearance. The ureter and pelvis of right kidney are distended with straw-colored fluid intermingled with brick-red, sand-like granules. This distention is due to the obstructing influence of the sand-like deposit in the distal portions of the ureter. The aorta is negative.

Microscopic Report.—Heart and Pulmonary Artery: Section made through the anterior wall of the pulmonary artery and attached vegetation shows fibrous thickening and moderate vascularity of adventitia, with numerous focal areas of leukocyte infiltration, chiefly of lymphocytes and plasma cells. The adjoining media exists as a narrow band adjacent to the adventitia, infiltrated with leukocytes, chiefly lymphocytes and plasma cells and focal collections of polymorphonuclear leukocytes; whereas the remaining portion of the media and intima are replaced entirely by products of inflammatory reaction, consisting of areas of frank purulent material, separated by an enormous amount of fibrin, red blood cells, and an occasional polymorphonuclear leukocyte. Within this inflammatory mass can be seen many intracellular and extracellular diplococci, of which a few are lancet-shaped.

Section through the pulmonary valve and adjacent wall of the artery shows proximally one-fourth of the valve to be markedly thickened, with dense, moderately cellular connective tissue, including many blood capillaries and spaces. Its concave surface is irregular and presents finger-like projections of connective tissue; whereas its convex surface is moderately smooth and irregular. The distal three-fourths of this valve is likewise thickened, with dense connective tissue, including numerous capillaries, and infiltrated with plasma cells. Both surfaces are irregular, showing projecting masses of fibrin, red blood cells and leukocytes, chiefly polymorphonuclear. The angle between artery and cusp is filled with a like inflammatory exudate.

Section through the pyramidal outgrowth of the tricuspid valves shows a central core of loosely arranged connective tissue, embracing capillaries and blood spaces and surrounded by a band of moderately dense connective tissue of varying thickness, infiltrated with an occasional lymphocyte. Overlying this dense band is the outermost lining of a single layer of endothelial cells.

Smears made from the cavity of the right lung show tubercle bacilli. Section through the apex of the right lung shows conglomerate tubercles. The liver shows sclerosis.

DISCUSSION

The heart, from a pathologic point of view, showed acute vegetations of pneumococcic origin, springing from the pulmonary valves and continuous with those that project from the wall of the pulmonary artery. The vegetations were so extensive that the lumen of the pulmonary artery was almost entirely obliterated. Aside from the acute reaction, the pulmonary valves showed diffuse and nodular types of sclerosis. The remaining valves likewise showed a diffuse sclerosis, whereas the tricuspid and mitral valves bore in addition the nodular type. The tricuspid orifice was somewhat dilated. The foramen ovale was patent. The right auricle and ventricle, especially the former, was markedly hypertrophied and dilated, whereas the left auricle and ventricle were apparently of normal size. The aorta was entirely negative. The liver presented a typical picture of the so-called chronic passive congestion. The lungs showed tuberculosis.

With the heart findings the question of utmost importance is whether the diffuse sclerosis of the heart valves was one of congenital or acquired origin, and if so, was there present prior to the pneumonic attack, a pulmonary stenosis? From the clinical findings, namely, clubbing of the fingers, bulging of the chest, slow mental development, cyanosis, etc., as manifested when the patient first came under our observation, and from the pathologic picture of the heart at necropsy, we were no doubt dealing with a process of diffuse sclerosis and pulmonary stenosis, the origin of which dates from the fetal state. A compensatory alteration, which was present in the heart and which is commonly held to indicate a congenital origin of stenosis of the pulmonary valves, is patulousness of the foramen ovale. An open foramen ovale alone does not indicate with certainty, in doubtful cases of pulmonary stenosis, that it is of congenital origin, but its patency, linked with other findings noted in the foregoing, substantiates our claim in assuming the congenital origin of the affection. Having then an obstruction and leak from earliest infancy in the pulmonary orifice, the physiologic pathology would be a lowering of the diastolic pressure with a subsequent increase of the pulse pressure in the pulmonary artery, accompanied by a greater systolic output from the right ventricle in order to compensate for the leak. When the strain is compensated, we have hypertrophy of the right ventricle, but when the strain becomes too great, dilatation follows. As a result of dilatation, functional insufficiency of the tricuspid valves sets in, thus throwing a tremendous load on the right auricle, which in turn hypertrophies and dilates, with final engorgement of the venous vessels of the neck and liver, causing, therefore, in the liver, passive congestion and ultimately sclerosis.

The enormously enlarged right auricle accounts for the clinical finding of a pulsating mass in the suprasternal notch. The presence of a pulsation, thrill and bruit in the auricle synchronous with ventricular systole, constituted, no doubt, the clinical manifestations of either a dilated tricuspid orifice, or incompetent tricuspid valves. The apparent diastolic shock, so often encountered in aneurisms, can be accounted for by the rapid emptying of venous blood from the right auricle through the tricuspid orifice and patent foramen ovale.

The question now arises, if blood escaped through the foramen during diastole, why was there not present at necropsy hypertrophy and dilatation of the left auricle? This can be answered by saying that pulmonary stenosis prevented the normal allowance of blood from passing through the pulmonary system. As a result, the pulmonary veins would likewise expel a relatively diminished quantity into the left auricle. In the case herein reported, the additional amount of blood received through the patent foramen ovale apparently adequately supplied the normal volume of blood, as was shown by the finding at necropsy of a normal sized left auricle and ventricle, and by the clinical manifestation of a radial pulse of good volume. If this were not true, that is to say, if normal equilibrium was not established, one would expect, on the one hand, a left auricle and ventricle reduced in size, together with a small radial pulse, or, on the other, hypertrophy and dilatation of the left auricle and ventricle with a strong radial pulse.

The murmurs heard previous to the pneumonic attack, synchronous with systole and diastole over the pulmonic area, were the clinical manifestations of pulmonary stenosis. It is denied by a number of writers, however, that a diastolic murmur is ever manifested in pulmonary stenosis, unless there is present an acute ulcerative condition. Nevertheless, Cantley[21] is of the opinion that a regurgitant murmur is present in most cases of pulmonary stenosis. He cites the case of a girl of 15 in whom there was present a double murmur in the pulmonic area. Several months later the patient developed rheumatic arthritis and died. Necropsy confirmed his statement. The pulmonary valves were found to be thickened and bore several acute vegetations.

Acute ulcerative involvement of a previously stenosed pulmonary orifice in most instances accentuates the pre-existent murmurs, especially the ones occurring synchronously with diastole. This clinical fact does not hold true in the case herein reported, for the reason that the enormous vegetation in the pulmonary artery almost entirely obliterated its lumen, thus producing a degree of obstruction in no wise inferior to that of the original stenosis.

As to what part the patent foramen ovale shared in the production of the murmurs heard, is a problem that we are unable to solve. If the patency produced murmurs, they must have been muffled by those resulting from the lesions of the pulmonary and tricuspid valves. It is possible that the diastolic murmur heard over the pulsating mass in the neck is in part a manifestation of this patency.

Tuberculous involvement of the lungs is quite common in all forms of pulmonary incompetency, and not infrequently is the terminal condition.

705 South Third Street.

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[21] Cantley, Ed.: A Case of Pulmonary Regurgitation, Lancet, London, 1902, **1**, 221.

PROGRESS IN PEDIATRICS

REVIEW OF THE LITERATURE OF THE PAST FIVE YEARS ON GONOCOCCUS VULVOVAGINITIS IN CHILDHOOD *

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This review comprises the most important articles on vulvovaginitis in children which have appeared during the past five years, with the exception of a few in foreign magazines to which we did not have access. Articles which consisted merely of a general description of the disease without any original observations were, as a rule, not included. A complete review of the literature from 1883 to 1912, by Generisch,[1] may be found in the Budapest *Medical-Surgical Presse* for 1911 and 1912.

CONTAGIOUSNESS

The extreme contagiousness of gonococcus infection among girls under puberty is universally admitted. As Meister[2] says, only a primary case is necessary in an institution; a little carelessness will do the rest, and when an epidemic has begun, only the strictest hygiene will prevent its rapid spread.

Hess[3] believes that it should not be regarded especially as an institutional disease, however, as it may be found in a considerable proportion of infants who live in crowded tenements in cities. Smith[4] notes that gonococcus vaginitis is confined largely to hospital practice, which would at once suggest that it is dependent, in part, at least, on poor social conditions. He also calls attention to the frequency with which feebleminded children act as centers of infection. This fact is an additional argument for their isolation, as such children are usually irresponsible in sexual matters.

Several factors are involved in this peculiar susceptibility of girls to gonococcus infection. Inclan[5] and Marshall[6] assert that the vaginal

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* Submitted for publication Jan. 30, 1917.

[1] Generisch, G.: Pest. Med.-Chir. Presse, Budapest, 1911, **47,** 405; 1912, **48,** 2.

[2] Meister, W. B.: Am. Jour. Obst., 1910, **61,** 540.

[3] Hess, A. F.: Am. Jour. Dis. Child., 1916, **12,** 466.

[4] Smith, R. M.: Am. Jour. Dis. Child., 1913, **6,** 355.

[5] Inclan, C.: Crón med.-quir. de la Habana, 1911, **38,** 422.

[6] Marshall, C. F.: Brit. Jour. Child. Dis., 1910, **7,** 385.

mucosa of small girls is especially susceptible to gonococcus infection, whereas in women the uterus and adnexa are more vulnerable than the vaginal mucosa. Maier[7] and Taussig[8] say that this susceptibility to invasion by the gonococcus is largely contributed to by the fact that the pavement epithelium of the vagina in early life is soft and tender and in reality more closely resembles the columnar than the pavement type.

An additional and important factor, noted by Taussig,[8] is the condition of the labia in early life. Not only are they devoid of the protective hair, but also are somewhat everted. With the increase in the size of the labia after puberty, and above all, with the development of hair, the vestibulum is shielded. Beyond the age of puberty no cases of vulvovaginitis have come to Taussig's clinic concerning whom there was any suspicion that infection had occurred other than by sexual contact. On the other hand, the great majority of infections under puberty are accidental and nonvenereal. Several authors note the frequency with which gonococcus vaginitis follows measles and scarlet fever. Louis Fischer[9] states that at times as many as 10 per cent. of the scarlet fever patients at the Willard Parker Hospital have this sequel or complication. Adkins[10] advances the theory that the desquamative changes which follow scarlet fever prepare the ground for infection with the gonococcus.

FREQUENCY AND INCREASE

Jeans[11] found that 5.3 per cent. of 262 girls over 1 year of age who applied for treatment of various maladies at the Children's Hospital, St. Louis, over a period of five months, were suffering from gonococcus vaginitis in various stages of the disease. Of 149 physicians replying to the questionnaire of the American Pediatric Society's committee on vaginitis,[12] less than 2 per cent. had observed any decrease in the number of cases seen during recent years, while from 13 to 28 per cent. had noted an increase both in private and hospital practice. Koplik[9] is authority for the statement that the disease is not as prevalent abroad as in this country, but ventures no explanation.

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[7] Maier, F. H.: Therap. Gaz., 1910, Series 3, **26,** 540.

[8] Taussig, F. J.: Am. Jour. Med. Sc., 1914, **148,** 480.

[9] Discussion of Barnett's Paper: Trans. New York Acad. Med., Sec. on Pediat., Am. Jour. Obst., 1913, **68,** 600.

[10] Adkins, W. N.: Atlanta Jour. Rec. Med., 1913, **60,** 267.

[11] Jeans, P. C.: Quoted by Taussig; see footnote 8.

[12] Fife, C. A., Gittings, J. C., and Carpenter, H. C.: Trans. Am. Pediat. Soc., 1915, **27,** 331.

ETIOLOGY

Smith[4] and Barnett[13] investigated the source of infection in forty-six and thirty cases, respectively, with the following results:

	Cases
Hospitals or other institutions	19
Playmates	4
Other members of the family affected, especially mother or sister	26
Assault	4
Undetermined	23

Spaulding[14] also investigated the source of infection in seventy-five patients treated at the vaginitis clinic at the Children's Hospital in Boston, but apparently includes a number of cases in which the diagnosis was not clearly established by bacteriologic methods.

In the report of the committee on vaginitis of the American Pediatric Society[12] appear the following estimates of physicians as to the probable source of infection in private practice. The figures indicate the number of times each cause was mentioned:

	Cases
Indirect contact with adult members of the household, probably not immoral	69
The toilet seat, or toilet articles (in 12 instances, the school toilet was specified)	53
Nurse or attendant	28
Direct transmission	8
Playmates	5
Clothing	5
Diapers or dressings	4

In the same report we find the results of the observations of social workers and visiting nurses among dispensary and hospital patients. Infection can be traced to:

	Cases
Other members of family	102
Hospital wards	107
Hospital dispensaries	1
Playmates	31
Sleeping arrangements	14
Toilet and bathing facilities	10
Public schools	8
Temporary institutions	13
Permanent institutions	1
Day Nurseries	5
Bad habits or character	15
Rape	8
Doubtful	93

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[13] Barnett, N.: Arch. Pediat., 1913, **30**, 650.

[14] Spaulding, Edith: Am. Jour. Dis. Child., 1913, **5**, 248.

In Taussig's[8] report of sixty-six cases, the mother was found to be infected in only two instances. He is inclined to suspect other girls and toilet seats much more frequently than the mother. While admitting that infected towels or clothes may play an etiologic rôle, he points out that the gonococcus quickly loses its virulence when dried, which fact would usually render such articles innocuous. Forty-seven of his sixty-six patients were of school age. This probably influences his conclusions.

Generisch[1] emphasizes the German idea that gonococcus vaginitis in girls owes its origin in some cases to the superstition that a man can be cured of gonorrhea by infecting a virgin.

Mitchell and Quinn[15] report an unusual instance of epididymo-orchitis in a boy of 6 months which caused a small epidemic of vaginitis in four girl patients in the same ward.

BACTERIOLOGY

Louise Pearce[16] states that although it is generally admitted that, both morphologically and by culture, different strains of gonococci seem to be identical, the use of the complement fixation tests shows differences in the power of various strains of gonococci to bind complement when monovalent antigens are used. In her studies she used freshly isolated strains of gonococci with one exception—a gonococcus under cultivation for seven years. Nine were so-called adult strains and six were infant strains. The latter were recovered from patients with vulvovaginitis under 5 years. There were also three strains isolated from cases of ophthalmia. Her conclusions were as follows:

> 1. Two principal types of gonococci may be recognized by suitable immunologic tests; for example, agglutination and complement fixation. These two types correspond to the adult and infant types of infection with the gonococcus, seen clinically.
> 2. On the basis of these immunologic reactions the strains of gonococci isolated from three cases of ophthalmia are classed with the adult type.
> 3. A polyvalent antigen for the serologic diagnosis of a gonococcus infection should represent strains of the infant type of organism in order that both types of infection, infant as well as adult, may be recognized.

In the discussion of her paper Pearce emphasizes the fact that these types are not absolutely clear cut and distinct, but that it is highly probable that gradations between the two types exist; that the gonococcus may be a more or less labile group within itself; and that if a large enough number of strains were tested by their immunologic reactions, certain of these would be found partaking of the characteristics of both types. This experimental evidence seems to corroborate the well recognized clinical difference between gonococcal infection as it occurs in infants and in adults.

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[15] Mitchell, A. G., and Quinn, N.: Arch. Pediat., 1915, **32,** 846.

[16] Pearce, Louise: Jour. Exper. Med., 1915, **21,** 289.

Meister[2] insists that failure to find the gonococcus in the vaginal discharge in a suspicious case means no more than failure to find the tubercle bacillus in the sputum of patients with tuberculosis. In cases in which the organism cannot be demonstrated, he recommends the application of a strong solution of silver nitrate to the vaginal mucosa, although the gonococcus should be cultured when possible. Norris[17] also uses a 5 per cent. to 10 per cent. silver solution in such cases, applied the day before the smears are to be made.

R. M. Smith[4] believes that cultures are required to establish the positive diagnosis of gonococcal vaginitis, although the presence of the typical organism in the smear, he admits, is the usual criterion.

G. G. Smith[18] believes that the examination of smears often gives inconclusive evidence. In many instances the gonococcus is undemonstrable, especially in chronic cases, and even if gram-negative diplococci are seen within the pus cells, their identity is not always certain. Even when there is no discharge and the smears are negative, the so-called negative phase or latent period, the discharge is prone to reappear. Martha Wollstein[9] also occasionally encounters patients admitted to hospitals during this latent period.

Norris[17] admits the difficulty of demonstrating the gonococcus in the chronic cases, and believes therefore that all suspicious inflammation of the vulvovaginal region during infancy and childhood should be treated as specific (gonococcal). Furthermore, he believes that the gonococcus is readily isolated during the acute stage of the disease.

Spaulding[14] concludes that all cases of vaginitis with a persistent discharge which at any time has been profuse, are due primarily to the gonococcus. She found that in some cases smears were positive for many months after the discharge had stopped, especially in those which had received treatment, whereas in others a positive smear was difficult to obtain even during the acute stage.

Hess[3] believes that when bacteria cannot be demonstrated, if numerous pus cells are found in smears taken from the cervix, the infective organism is the gonococcus in the overwhelming majority of cases.

In the report of the American Pediatric Society[12] the summary of the opinion of thirty-seven bacteriologists is of interest. Approximately one third believe that identification is possible by observation of the morphologic and staining characteristics of the organism and by observation of its relation to other structures in the smear preparations; that is, by the fact that the gonococcus is an intracellular, gram-negative biscuit-shaped diplococcus. However, one half are of the opinion that the diagnosis may be safely made when such organisms predominate; when they are found in a profuse discharge from a situation susceptible of infection with the gonococcus; and when pus cells are present in proper position to the bacteria, especially when they show an increase of acidophilic granules. Three fourths of the bacteriologists believe that the percentage of error in this method of examination is very small. About one-third require typical cultural reactions in addition to these morphologic characteristics in order to fix the identity of the organism; one half of these advocates of the cultural method of differentiation demand it, regardless of the clinical history and physical signs, or of the evidence gained from coverslip preparations.

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[17] Norris, C. C.: Jour. Am. Med. Assn., 1915, **65**, 327.

[18] Smith, G. G.: Am. Jour. Dis. Child., 1913, **5**, 313.

The cultural characteristics most commonly insisted on are: The organism should not grow on ordinary mediums, but readily develop on ascitic, hydrocele or blood agar at body temperature, with the formation in ascitic agar of moist, tiny, transparent, drop-like colonies of gram-negative diplococci of short longevity. These colonies should have thin, irregular, elevated edges and a crumb-like appearance on the center of growth. The culture must ferment dextrose, but no other forms of sugar. The pure culture does not affect ordinary test animals.

The technic of obtaining material for the smears is a matter of great importance. Barnett,[13] for example, found that smears taken from the fornix might be positive, whereas smears taken from near the hymen were negative. Willcox[9] prefers that smears be taken from the vault of the vagina and cervix, and Martha Wollstein[9] asserts that only by observing care to secure material from the inside of the vagina can extraneous contamination be avoided.

Van Gieson[19] states that the real value of the detection of the gonococcus is found at the very beginning and in the declining stages of the discharge. The intact leukocytic cell body is a sine qua non in diagnosis. Van Gieson finds that the cotton swab ordinarily used in making smears distorts the leukocyte and may injure the mucous membrane. Therefore he advocates the use of a medicine dropper and a 1:5,000 solution of mercuric chlorid in securing specimens for examination. The solution is injected into the vagina and drawn back into the dropper several times. It is then centrifuged and the sediment examined for cells and organisms. By a contrasting table he shows the efficacy of this method as compared with the usual moist or dry swab.

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[19] Van Gieson, I.: Med. Rec., New York, 1910, **77,** 1001.

Norris[17] and Adkins[10] advocate this method of Van Gieson's. G. G. Smith[20] and Spaulding[14] prefer the use of the platinum loop.

Sinclair,[21] following the method of Rubin and Leopold,[22] used the electrically lighted female urethroscope in the diagnosis of gonococcus vaginitis in eighty-three infants. Smears were made through the urethroscope, from the cervix and vaginal mucosa. The platinum loop gave the best results, the moist swab was less satisfactory and the dry swab was much inferior. Van Gieson's irrigation method did not give as reliable results as the use of the urethroscope. Among the eighty-three cases, sixteen were found to be infected or highly suspicious on admission. Of the sixteen cases, 21 per cent. would have escaped detection without the use of the urethroscope, and only 30 per cent. showed any visible signs of discharge. The characteristic tendency of the disease to assume periods of latency is misleading.

Barnett[13] used a Skene urethral speculum and head mirror, as suggested by Koplik in 1893, in the diagnosis of vulvovaginitis, but later the Kelly electrically lighted endoscope was used. He also prefers the platinum loop for obtaining material for smears from the walls and floors of the vagina.

COMPLEMENT-FIXATION TEST

G. G. Smith,[18] in 1913, described the complement-fixation test as a serum reaction highly specific for gonorrhea. It is similar to the Wassermann reaction in syphilis. In a study of twenty-five cases, Smith found a positive complement fixation in eleven of twelve clinically positive cases, and in four cases in which the clinical evidence was inconclusive. In two of these four cases there had been no discharge for one and two years and smears were negative. The test was negative in three cases in which other evidences of cure were insufficient, but in seven others the clinical findings were corroborative. A year later Smith[20] published a further report on sixteen of these cases. Of nine, in whom there had been no recurrences and who gave negative complement-fixation tests in 1913, all but three gave weekly positive or suspicious reactions in 1914. This he explains by the greater sensitiveness of the tests which has developed from further use. Of seven patients who gave positive tests a year before, five were clinically well and two showed some discharge in which the gonococcus could not be demonstrated. Of the five which were apparently cured, two showed a weakly positive complement fixation; one a moderately positive reaction and two were negative. So strong is Smith's belief in the complement-fixation test that he interprets an absolutely negative result as proof of the absence of gonococcus infection.

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[20] Smith, G. G.: Am. Jour. Dis. Child., 1914, **7,** 230.

[21] Sinclair, J. F.: Arch. Pediat., 1914, **31,** 29.

[22] Rubin, I. C., and Leopold, J. S.: Am. Jour. Dis. Child., 1913, **5,** 58.

Other authors are less didactic. Norris[17] believes that complement fixation and cutaneous tests are diagnostic if positive and carried out by an expert bacteriologist. Negative tests, however, do not rule out gonorrheal infection. Barney[23] looks on a moderately or strongly positive complement fixation as confirmatory proof in doubtful cases, and R. M. Smith[4] also considers it as a valuable aid in diagnosis. Kolmer[21] found only 50 per cent. of positive results in ten of Sinclair's cases, in which the diagnosis had been made with the aid of the urethroscope.

That the apparent vagaries in the results of complement-fixation tests may depend on the degree of involvement can be seen from the following:

Thomas, Ivy and Birdsall,[24] using specific and nonspecific antigens, failed to find a positive gonococcus complement fixation in adults when the vagina alone was involved. Williams[25] also states that gonococcus infection must reach at least the level of the uterus before a positive reaction occurs. Most of his patients were adults.

Schwartz and McNeill[26] also find that in adults the infection must involve the cervix before complement fixation is positive. In ten patients under 5 years of age the complement-fixation test was negative.

McNeill,[27] in another communication, reports the result of complement-fixation tests in eight children who had had gonococcus vaginitis from one to three years. Six had no discharge at the time the tests were made. Five gave a four plus positive reaction; two a double plus and only one a one plus. These results, few as they are, nevertheless show that infantile vulvovaginitis may be more than a local infection and that the general infection may be active after all local manifestations have disappeared. In acute cases when the complement-fixation test is negative, antigens may be prepared from pure cultures of the suspected organism and tested against a known antigonococcus serum.

Irons and Nicoll[28] obtained a positive complement fixation in seven cases of gonococcus vaginitis and negative results in five cases. In another series of five cases in which the gonococcus was obtained by culture, four showed a positive complement fixation. They investigated a third series of seventeen patients who were suffering from scarlatina or diphtheria. All of these showed typical gonococci in smears, and some were also proved by cultural methods. Five of these seventeen cases gave a positive complement fixation, ten were negative and two were weak or doubtful. In one case with a purulent discharge in which no gonococci could be demonstrated, a positive complement fixation was obtained. In two cases in which a colon bacillus and a diphtheroid organism were found, the complement-fixation test was negative. They consider that, as a means of detection of gonococcus vaginitis, the complement-fixation test has a limited value. Positive reaction cannot be expected in early infection, and probably not even in cases of long standing, unless there is deep involvement. A negative reaction, therefore, is inconclusive.

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[23] Barney, J. D.: Boston Med. and Surg. Jour., 1916, **174,** 740.

[24] Thomas, B. A., Ivy, R. H., and Birdsall, J. C.: Surgery, Gynec. and Obst., 1914, **19,** 390.

[25] Williams, W. W.: Interstate Med. Jour., 1914, **21,** 1198.

[26] Schwartz, H. J., and McNeill, A.: Am. Jour. Med. Sc., 1912, **144,** 815.

[27] McNeill, A.: Arch. Pediat., 1913, **30,** 657.

[28] Irons, E. E., and Nicoll, H. K.: Jour. Infect. Dis., 1915, **16,** 303.

The majority of bacteriologists who replied to the questionnaire of the American Pediatric Society[12] consider that the complement-fixation test is of decided value: when it is performed by a skilled serologist with satisfactory antigen and adequate controls; when the infection involves the deeper structures, and when it has been of duration long enough to cause the production of specific amboceptors.

PATHOLOGY

Sinclair[21] and Barnett[13] describe the lesions of vulvovaginitis found on a vaginal examination with the urethroscope. In most cases a small amount of dried pus was found on the labia, and pus was seen coming from the vagina, but the external appearance of the hymen might be normal in a pronounced gonorrheal process. The vagina was a dull pink color, with pus in the rugae and, occasionally, hemorrhagic spots. The cervix showed marked changes, being deeply congested, with pus exuding from the cervical canal. Superficial ulceration of the cervix was occasionally observed. In 30 per cent. of Barnett's fifty cases ardor urinae was present.

Hess[3] states that postmortem examinations show that in the subacute and chronic cases of vaginitis in infants the cervix is most frequently involved, and that the vagina generally shows no signs of inflammation. Cervicitis would therefore seem to be a more correct term than vaginitis. Kenessey[29] performed complete necropsies on two children who had gonococcus vaginitis and had died of pneumonia following varicella. In both cases a gram-negative intracellular diplococcus was found in the material within the uterus, and in the second case this organism was isolated in hydrocele agar. From the pathologic findings in these cases he concludes that the gonococcus in childhood can invade not only the uterine cavity, but also the tubes and ovaries. Further, that the adnexa can be so severely involved as to cause irreparable damage to their later function.

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[29] Kenessey, A.: Pest. Med.-Chir. Presse, Budapest, 1913, **49**, 360.

COMPLICATIONS

Meister[2] finds that in infants suffering from gonococcus vaginitis complications are usually few and not serious — such as local dermatitis and enlargement of the inguinal glands. In older girls, on the other hand, any of the complications common to gonococcus infection in the adult may occur, including endometritis, salpingitis, peritonitis and, occasionally, endocarditis and pericarditis and arthritis. With this opinion the majority of observers seem to be in accord.

Perrin[30] believes that the rudimentary stage of development of the uterus and tubes in little girls explains the rarity of their involvement. Barney,[23] noting that the Bartholin and the Skene glands are undeveloped in childhood, as well as the uterus and tubes, ascribes to this fact that blood-borne metastases are rarely seen. Without specifications as to the age of the children, Marshall[6] and Spaulding[14] believe that gonococcus vaginitis, however contracted, may be followed by the same complications as in adult life.

Danger of infection of the eye seems to be much greater in early life than in adult life. Adkins,[10] who has never encountered a case of gonococcus arthritis, has seen quite a few infections of the eye complicating vaginitis. Van Gieson[19] also considers ophthalmia a serious danger.

Chapin's[9] experience has been more fortunate. He has rarely seen infection of the eye, and only one instance of tubal involvement. To offset this we have the following:

Marfan and Debre[31] report in extenso the case of a girl, aged 10½ years, suffering with chronic gonococcal vulvovaginitis, who developed symptoms of pelvic peritonitis and, afterward, endo-pericarditis and pleurisy. The most interesting fact was the recovery from the blood, by culture, of the gonococcus.

Schwers[32] records the case of a child 2½ years old in whom tenosynovitis of both arms, spondylitis and arthritis of the right sternoclavicular articulation and a polymorphous eruption were observed in the course of an acute attack of vulvovaginitis. Recovery ensued without treatment.

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[30] Perrin, T.: Allg. med. Centr.-Ztg., 1910, **79,** 773.

[31] Marfan, A. B., and Debre, R.: Bull. et mém. Soc. méd. d. hôp. de Paris, 1910, Series 3, **29,** 712.

[32] Schwers, H.: Arch. de méd. d'enfants, 1914, **17,** 355.

Koplik[9] has known of four instances of fatal gonococcic peritonitis in the course of vaginitis occurring in patients at the Mt. Sinai Hospital, New York City.

Thirty-nine per cent. of the physicians who answered the questionnaire of the American Pediatric Society[12] have seen more or less severe systemic complications such as pus tubes, arthritis, pelvic or general peritonitis, septicemia, endocarditis, ophthalmia, etc., occurring in sixty or more cases.

We may sum up the actual proportion of complications to cases treated in the following reports of physicians who have made a special study of gonococcal vaginitis: Barnett,[13] 50 cases; Taussig,[8] 66 cases; Comby and Condat,[33] 18 cases; Sinclair,[21] 33 cases; Hamburger,[34] 21 cases; a total of 188 cases.

Complications	Number of Cases
Arthritis	3
General peritonitis	2
Pelvic peritonitis	2
Tubal infection	6
Ophthalmia	4
Periosteal disease of heel	1
Proctitis	3
Intense dermatitis of vulvae and thighs	2
Urethritis	1
Inguinal adenitis	1

Number of instances of complications, 25.
Percentage of cases showing complications, 13.3 per cent.

SEQUELAE

Whitehouse[35] suggests that some cases of endometritis, salpingitis and dysmenorrhea in the adult may be due to latent, uncured gonorrhea in childhood. Spaulding[14] has been unable to substantiate this, and Koplik[9] has had under observation several patients who had gonococcic vaginitis during childhood and who afterward married and were able to bear children. In the report of the American Pediatric Society[12] we find that only three of the gynecologists have treated adults who were known to have had gonococcus vaginitis during childhood. One has seen no sequelae, the other two have had to operate, one for pelvic peritonitis, and the other for peritonitis, salpingitis and oöphoritis. Although so few have seen instances in which vaginitis during childhood has manifested itself by sequelae in later life, 30 per cent. of the twenty gynecologists who expressed an opinion, positively state that gonococcus vaginitis of childhood may last after puberty; 40 per cent. more or less qualify their affirmative reply; the remaining 30 per cent. either definitely deny or gravely doubt its persistence.

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33. Comby, J., and Mlle. Condat: Arch. de méd. d'enfants, 1914, **17,** 419.
34. Hamburger, R.: Deutsch. med. Wchnschr., 1914, **40,** 759.
35. Whitehouse: Practitioner, London, 1910, **84,** 485.

TREATMENT

Treatment of gonococcus vaginitis in children involves the use of local remedies and vaccines, and general constitutional measures. Most authors make use of some form of local treatment, some few believing that persistence in a reliable technic will result in cure, although admitting that much time and patience are requisite. Wolff[36] opposes local treatment in those past infancy on the score of its demoralizing influence. Rygier[37] enlarges on its difficulties and the lack of permanent results.

Adkins[10] believes that the disease runs its course in spite of all one can do to cure it. Certain local measures he finds of temporary benefit. Among these is the injection of suspensions of living lactic acid bacilli.

Whitehouse[35] also has treated eight patients with cultures of lactic acid bacilli without the use of other measures. He obtained cessation of discharge and disappearance of gonococci and septic organisms in from fourteen days to three weeks. He does not know whether or not these results are permanent, however.

Taussig[8] believes in rest and general tonic treatment. He does not believe in irrigations, but prefers instillations of a solution of argyrol, 25 per cent., in the early stages; later a 1 per cent. to 4 per cent. solution of nitrate of silver.

G. G. Smith[20] advocates mechanical cleanliness by means of irrigations with potassium permanganate, 1:4,000, and the prolonged use of silver salts, such as argyrol. He continues these treatments for one month after all discharge has disappeared.

Perrin[30] has treated over 100 cases during the last ten years with injections of protargol 5, water 8, glycerin, q. s. ad. 50. He claims that all were radically cured within fourteen to twenty days. Most of the cases were chronic and had received a variety of other forms of treatment.

The most elaborate technic is described by Norris[17] as follows: The child is put in the Sims or knee-chest position. The hymen usually must be sacrificed. The vagina is washed with weak potassium permanganate solution and swabbed with 25 per cent. argyrol solution. It is then thoroughly dried with strips of gauze, and the drying completed with an empty atomizer. The child is kept in the Sims position for twenty to thirty minues to allow air to enter the vagina. Finally the vagina is flooded with a weak solution of silver nitrate, gradually increased in strength, and glycerin added. The above treatment is carried out three times a week. In the interim the mother or nurse uses a weak permanganate or argyrol solution introduced with a soft

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36. Wolff, M.: Chicago Med. Recorder, 1913, **35,** 462.
37. Rygier, S.: Deutsch. med. Wchnschr., 1911, **37,** 2334.

rubber ear syringe. By this method Norris cured fourteen patients in an average of twelve weeks, the longest time being eighteen weeks.

Willcox,[9] after trying all methods of treatment, believes that the disease is controlled but not cured. Fisher[9] has abandoned treatment other than the use of irrigations of magnesium, alum and water. He also advocates the use of general tonic treatment, namely, change of air, arsenic, cod liver oil and iron.

Rubin and Leopold[22] insist on the importance of determining the extent of the deep lesions before beginning treatment. For this purpose the electrically lighted female urethroscope should be employed. When irrigations are resorted to, the douche tip should enter the vagina for at least 1½ inches. Applications by swabs used without the urethroscope are injurious and useless. When strong silver solutions are applied to the cervix and vagina, it is well to keep the child in bed for a few days.

Barnett[13] also advocates the use of the electrically lighted urethroscope in treatment in order to apply the medicament directly to the cervix. This he considers important, as the involvement of the cervix is not easily amenable to the ordinary douche or irrigation. He prefers Lugol's solution 1: 500. With the use of the urethroscope he obtains a cure in a month; whereas at the end of six months only seven of his twenty-six patients undergoing prolonged systematic treatment were cured by ordinary irrigations.

Freeman[9] states that local treatment should not be limited to one method, as a change often brings good results. He also believes in the use of the endoscope.

Kerley[9] sounds a timely warning that a large number of cases should be studied before reporting results from any form of treatment, as occasionally a run of mild infections occurs and the physician, in such an event, would become unjustifiably enthusiastic about his method of treatment.

VACCINE TREATMENT

One of the most ardent advocates of the use of vaccines is B. W. Hamilton,[38] who treated eighty-four patients with 90 per cent. of cures in an average time of fifty days. These figures he contrasts with 260 patients treated by irrigation alone, in whom there were 60 per cent. of cures in an average time of 300 days (ten months). He used two stock vaccines and one freshly prepared from an eighteen-hour blood agar culture taken from an adult male with urethritis. He describes at length his method of administering vaccines. Apparently, local treatment was not used.

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[38] Hamilton, B. W.: Am. Jour. Obst., 1910, **61**, 837.

Wolff[36] believes that gonococcus vaginitis is one of the diseases in which vaccine treatment has proved itself to be especially advantageous if given in a careful and judicious way. Stock vaccines do not show a constant efficiency and have no scientific basis. Vaccines should be made from fresh cultures, and should include the organisms ordinarily found in conjunction with the gonococcus, namely, staphylococcus, diplococcus (not gonococcus) colon bacillus, pseudodiphtheria bacillus. Wolff treated with vaccine forty patients from 1 to 14 years of age, without local measures other than external cleanliness. Many of the cases were chronic. The number of injections varied from four to ten, with an average of seven, injections being given every five to seven days. After one year only one case is known to have relapsed. He believes autogenous vaccines to be 100 per cent. efficient.

Another strong advocate of vaccine treatment is W. J. Butler,[39] who has reported several series of cases treated with monovalent and polyvalent stock vaccines; the former he usually finds more efficacious. His results, without local treatment, show 75 to 85 per cent. of cures in from ten days to two months, in both acute and chronic cases. By cure he means the disappearance of discharge, and "several" negative smears. He finds the vaccine treatment incomparably more efficient than local treatment, and hopes that the latter will be abandoned except in rare instances.

Rygier[37] used a stock vaccine made from many strains of gonococci, and believes that vaccine treatment offers greater certainty and rapidity of cure than any other known method.

Comby and Condat[33] treated 18 patients with the vaccine of Nicolle. Marked improvement was noted after the second injection, but no data are given as to the subsequent course. They believe that the results from vaccine compare very favorably with those from local treatment, with the added advantage that local treatment is unnecessary except in unusually stubborn cases.

Spaulding[14] used autogenous vaccines in conjunction with various forms of local treatment. She believes that vaccines are not specific, but an added factor for good.

Whitehouse[35] noted disappearance of all symptoms in two cases after the fifth and sixth injections of vaccine, and Adkins[10] reports good results in a series of thirty-two cases.

Strassberg[40] believes in vaccine in the early stages, before many forms of local treatment have been used. Later he advocates both local and vaccine treatment.

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39. Butler, W. J.: Interstate Med. Jour., 1910, **17,** 510.
40. Strassberg, M.: Wien. klin. Wchnschr., 1914, **27,** 889.

Carrau[41] used the vaccine of Nicolle and Blaziot[42] in fifteen patients, five to twelve years of age, without any local treatment. In only two did the gonococcus disappear, although the discharge diminished markedly in all the others.

Cecil[43] used a sensitized vaccine, that is, a vaccine treated with specific homologous serum, with satisfactory results. Some of his patients were adults, however, so that the figures are not available as they apply to children.

Barnett[13] could find no improvement in the vaginal discharge in patients treated with vaccines, but the complication of arthritis yielded rapidly.

Tieche[44] notes the danger of "sexual trauma" from the use of local treatment, but concludes that the combination of vaccines and local measures offers the best hope for cure.

Boas and Wulff[45] treated twenty-six patients, two with vaccine alone, seven with vaccines and local measures, and seventeen received only local treatment. The best results were obtained with the combined treatment. The two patients treated by vaccine alone quite certainly showed no improvement.

The toxicity of gonococcal vaccines is considered an almost insurmountable obstacle by Murphy and Kreuscher,[46] although Nicolle and Blaizot[42] claim they have succeeded in entirely overcoming this toxicity and in rendering the vaccines stable.

Marfan and Debre[31] found Wright's vaccine inefficacious. Hamburger[34] has used stock vaccines in the treatment of twenty-one children. He fails to state his definite results, which evidently were unfavorable.

G. G. Smith[20] does not believe that results with vaccine are satisfactory in gonococcus infection of the mucous membranes either of the male or female.

Freeman[9] is inclined to believe that vaccines have done little if any good.

Kerley[9] used stock vaccines in thirty-six cases without any noteworthy results.

Wollstein[9] has used both autogenous and stock vaccines, according to the opsonic index. The results were not encouraging.

Of pediatricians who answered the questionnaire of the American Pediatric Society[12] as to the use of vaccines, twenty favored it and

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41. Carrau, A.: Rev. med. d. Uruguay, Montevideo, 1915, **18,** 79.
42. Nicolle, C., and Blaizot: Jour. d'urol., 1913, **4,** 734.
43. Cecil, R. L.: Am. Jour. Obst., 1915, **72,** 528.
44. Tieche: Cor.-Bl. f. schweiz. Aerzte, 1912, **42,** 159.
45. Boas, H., and Wulff, O.: Hospitalstidende, 1910, 5 R., p. 801.
46. Murphy, John B., and Kreuscher, P. H.: Interstate Med. Jour., 1914, **21,** 1214.

eleven found no material benefit from it. Approximately two thirds of the bacteriologists throughout the country also favored its use. The majority favored the use of autogenous vaccines, or, in the event that such were not available, some sanctioned the use of polyvalent stock vaccines. About four fifths of the bacteriologists believe that, if vaccines are properly made and administered, they are free from danger. The remaining fifth deny that they are harmless.

OPSONIC INDEX

Hamilton[38] could find no relation between the opsonic index and the activity of the vaginal discharge, while using vaccine treatment.

Wolff[36] believes that the determination of the opsonic index is not essential if care is taken to regulate the dosage of vaccine by the reaction and the clinical needs of each individual case.

Butler[39] originally controlled the administration of vaccine by the determination of the opsonic index, but abandoned it after finding the proper dosage and interval. He advocates small doses, 5 to 50 million at first, repeated at five-day intervals.

The only reference found to the use of serum in the treatment of gonococcus vaginitis was that by Marfan and Debre,[31] who used antimeningococcic serum subcutaneously. Unusual and grave anaphylactic symptoms resulted.

DURATION AND LATENCY

The tendency toward chronicity of gonococcus vaginitis in children is one of its most noteworthy and generally admitted characteristics. As Adkins[10] says, a consideration of the well-known chronicity of the disease in adults would give sufficient grounds for a like expectation in children. The tendency toward latent periods followed by recurrences is more marked in children.

Barnett,[13] in studying fifty cases, found that the duration of the disease, according to the history, varied from one week to several years. One case had existed for six years, with gonococci present in the vaginal pus. The average duration was eight and one-half months. In twenty-six cases, Spaulding[14] found the average duration was twenty months. The disease, she believes, may extend over many years, during which time there may be many recurrences and the periods of latency may be as long as eighteen months.

Rubin and Leopold[22] believe that the cause of the chronicity of gonococcus vaginitis in children lies in the anatomic construction which does not permit of free drainage. This is not due to the hymen, but to the fact that each segment of the vagina serves as a valve to dam back the discharge, as the vaginal walls are constantly in close contact.

Then, too, the vaginal portion of the cervix shows the most marked changes, and, at the same time, is in the most disadvantageous position for drainage and treatment.

R. M. Smith[4] gives the following results in thirty cases: Cured, 8 (no symptoms for from three to twenty-four months); 4 negative complement-fixation tests; under treatment from one and one-half to twenty-one months; did not continue treatment, 14; still under treatment, 8 (from one month to two years).

Barnett[13] found that the discharge soon ceased with any method of treatment. This, however, did not constitute a cure, as smears may remain positive for months after all visible signs of discharge have ceased.

Kerley[9] notes that cases clear up spontaneously after an indefinite course, due to the attenuation of the organism. This explains the comparative rarity of a course extending beyond the third or fourth year.

Koplik[9] also believes that the disease is self-limited.

CURE

R. M. Smith[4] thinks that the disappearance of all symptoms, after adequate treatment, with persistent negative smears and negative complement fixation, is a fair indication of a cure. The reappearance of a discharge in such patients, when the original source of infection persists and there has been no reform in the habits of the patient, is more likely to be a reinfection than a relapse.

G. G. Smith[18] believes that when other signs point to a cure, the complement-fixation test should be used as a court of last appeal. If a case proves to be a cure, with a negative complement fixation, Smith also believes that a recurrence of discharge containing the gonococcus signifies a reinfection and not a relapse.

Spaulding[14] believes that the most efficient treatment does not insure a permanent cure. She found that twenty-four of twenty-six patients had a recurrence of the discharge after apparent cure, in from three weeks to six years. Apparently she does not consider the possibility of reinfection!

The criteria on which it is believed that a cure can be predicated may be summarized as follows:

Barnett[18] and Wolff[36] base a cure on three negative smears taken at weekly intervals after all treatment has been stopped.

Maier[7] demands an additional fourth smear after a three-weeks' interval — six weeks in all.

Hamilton[33] requires four negative smears at weekly intervals and two additional smears at two-week intervals, eight weeks in all.

Norris[17] bases a cure on three negative bacteriologic and physical examinations made at intervals of two weeks, the last examination being preceded by chemical irritation with a nitrate of silver solution.

PROPHYLAXIS

Smith[4] believes that we must recognize that we are dealing with a social evil, and that the medical treatment is only a part of what needs to be done in the attempt to eradicate the disease. Parents must be made to recognize the contagiousness of the disease if we are to utilize one of the most important factors in preventing its spread.

Hess[3] states that vulvovaginitis is another instance of the healthy but dangerous "carrier," which is emphasized by the difficulty in recognizing the latent cases. By means of a provocative inoculation of gonococcus vaccine he has been able to convert the concealed "carrier" into the "open" case, and in this way to discover many cases which had eluded detection. Furthermore, he believes that the inoculations have some prophylactic value, and that they either confer protection or render subsequent infection of a mild character, so that it assumes a bacteriologic rather than a clinical type.

Spaulding[14] believes that the physician should realize the importance and prevalence of the disease and institute stricter preventive measures, both in hospital and private practice.

Adkins[10] notes that the negro child nurses in the South commonly are infected with the gonococcus, and believes that there should be a law compelling nurses to undergo examination. He advocates the use of silver salts in the vagina immediately after birth, and believes that the vagina is even more liable to infection than the ocular mucosa.

Taussig[8] also advocates the prophylactic injection of a drop of 2 per cent. solution of silver nitrate into the vestibulum vaginae in all new-born infants, when there is any evidence of gonorrhea in the mother. He advocates making gonococcus infection reportable to the health authorities, the education of mothers, and most important of all, the adoption of the U-shaped toilet seat with the low bowl in all public lavatories, schools, tenements, play-grounds, etc.

Meister[2] also advocates the use of a 2 per cent. solution of silver nitrate in swabbing the labia and vagina of new-born girls, followed by an irrigation with a saturated solution of boric acid.

It is generally admitted that the routine examination of girls before admission to an institution should include determination of the presence or absence of gonococcal infection.

Willcox[9] states that at the Bellevue Hospital, New York, girls are kept in the detention ward for three days while smears are taken daily from the cervix and vaginal vault. Absence of pus cells and organisms must be shown before the child is admitted to the wards.

In an editorial in the *Lancet*[47] attention is called to the variable incubation period in true gonococcus vaginitis, which may be as long as three weeks. There is, therefore, constant danger of the introduction of the contagion into general wards even when a negative smear has been obtained on admission.

Butler[39] insists on isolation, especially because one attack does not confer immunity against reinfection. He also insists that the disease is acquired by infection of the genitals. The usual sources he believes to be the common bath tub, common toilet and the hands of the nurse. He does not believe that the laundry plays any part in epidemics.

G. G. Smith[20] advocates allowing children to go to school if the mother is warned not to let her child use the toilet.

Sinclair[21] believes that a campaign of education should be carried out, especially in the home and in all kinds of institutions dealing with the various phases of child welfare, such as day nurseries, asylums, hospitals, public bathhouses, recreation centers, schools, etc. He also advocates the systematic examination of all inmates of institutions, including lay helpers; the establishment of special clinics in hospitals; and that boards of health should be empowered to make gonorrhea a reportable disease. Barnett[13] also subscribes to most of these precautionary methods.

The opinion of physicians who replied to the questionnaire of the American Pediatric Society[12] as to the importance of various prophylactic measures is shown as follows:

	Points
1. Hospital care Under this heading are included, isolation, prolonged treatment till cured, improved technic in handling and in treatment, special instruction to nurses, especially night nurses, etc.	88
2. Instruction to the laity Under this heading are included printed and verbal instructions as to the nature of the disease, danger of transmission, best means for prophylaxis, etc.	52
3. Schools Examination and exclusion of positive cases, care as to the toilets, etc	20
4. Control by boards of health Compulsory report of cases, compulsory treatment, etc.	16
5. Physicians Instruction as to the importance of early recognition, prolonged treatment, etc.	15
6. Institutions and tenements Adequate medical supervision, care as to toilets, etc.	11
7. Medical-sociologic relief Systematic sociologic study, follow-up nursing, etc.	7

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[47] Editorial: Lancet, London, 1910, **2**, 1354.

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OCCLUSION OF THE AQUEDUCT OF SYLVIUS IN RELATION TO INTERNAL HYDROCEPHALUS *

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The object of this report is to present with all possible accuracy the results of the clinical, postmortem and histologic investigations in eight cases of internal hydrocephalus of the obstructive type, bringing special emphasis to bear on the obliterating lesion of the aqueduct of Sylvius as a cause of ventricular distention.

Of this group, examined without selection, all show either complete occlusion of the aqueductus cerebri or obliteration of the fourth ventricle through severe pathologic changes occurring in the ependymal or subependymal tissues of these regions.

The first four cases have already been shown before the New York Pathological Society[1] and the records reappear at this time in greater detail, together with the findings in four other cases not reported heretofore.

Beside the congenital, obstructive form of the disease as it appears in this review, a subdivision of this type of hydrocephalus occurs apparently idiopathically, in previously healthy young adults and older children, in which occlusion of the aqueduct may readily be made out in histologic sections. In such cases it is probable that a predisposing constitutional weakness has existed from the earliest time and that the ependymal cells have been stimulated by some local factors to excessive formative activity, so that gliosis, with consequent closure of the iter, takes place.

Although interference with the normal passage of cerebrospinal fluid, whether due to mechanical obstruction or to some pathologic change in the ependyma or more deeply lying structures of the aque-

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[1] Proc. New York Path. Soc., 1911, **11,** 64.

duct, figures in the development of hydrocephalus, many cases have been recorded wherein no such factor can be made out. Similarly, the generally accepted idea of an obstruction to free communication between the ventricles, and between the ventricles and the general subarachnoid space, implying closure of the foramina of Magendie and Luschka, and in some cases of unilateral hydrocephalus, closure of the foramen of Monro, cannot be verified in pathologic studies of these conditions.

This variety of hydrocephalus offers an opportunity for further study of the origin, the removal, and hindrance to the normal movement of the cerebrospinal fluid.

The recently published studies of the cerebrospinal fluid by Weed and by Wegefarth, with an introduction by Cushing[2] consider this phase of the question in comprehensive manner, while the contributions of Frazier,[3] and of Frazier and Peet,[4] based on clinical and laboratory observation, have done much to enlighten us with respect to those problems which have long resisted solution.

Dandy and Blackfan[5] also in a report of their clinical and experimental work on hydrocephalus discuss the subject of the origin and disposition of the cerebrospinal fluid. Dixon and Halliburton[6] go into the points in question and give the results of their investigations dealing with the effects of extracts of the choroid and other glands on secretion of the choroid plexuses.

The surgical aspect of the subject has been well reviewed by Haynes,[7] who gives a detailed account of the physiology of intracranial pressure, discussing the modes of production and escape of fluid from the cavities of the brain.

Referring to the older literature on the subject, we find that L. W. Weber,[8] in summing up the pathologic considerations in a number of cases, came to the conclusion, not greatly at variance with present-day ideas, that three mechanical factors figure prominently in the production of hydrocephalus:

First, an increased fluid production due to inflammatory changes in the choroid plexuses, the ependyma and brain substance as well as obstructive processes in the choroidal vessels.

Second, impediment to the outflow of cerebrospinal fluid, via the venous and lymphatic channels, besides the obstacle of a frequently existing chronic, diffuse leptomeningitis, causing an impermeability of the subarachnoid spaces.

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[2] Weed and Wegefarth: Jour. Med. Research, 1914, **31,** 21.

[3] Frazier: Jour. Am. Med. Assn., 1915, **64,** 1119.

[4] Frazier and Peet: Am. Jour. Physiol., 1914, **35,** 268.

[5] Dandy and Blackfan: Jour. Am. Med. Assn., 1913, **61,** 2216.

[6] Dixon and Halliburton: Jour. Physiol., 1914, **47,** 215.

[7] Haynes: Ann. Surg., 1913, **57,** 449.

[8] Weber, L. W.: Arch. f. Psychiat., Berlin, 1906, **41,** 61.

Third, lessened resistance of the ventricular walls due to inflammatory, degenerative or sclerotic processes in the affected areas. Weber believes that these three cardinal factors are operative in both acquired and congenital hydrocephalus, but that in the case of congenital disease the second element is present to a greater degree, while in the acquired form increased fluid production plays the more important rôle.

In the matter of diminished resistance of the walls of the ventricles in congenital hydrocephalus, Weber contracts the natural pliability of the fetal brain with the general or localized diseased condition of the brain substance in cases coming on later in life when dilatation may be symmetrical or confined to one, or to a portion of one, ventricle.

In that form of hydrocephalus characterized by hypersecretion, Gowers[9] has so frequently found meningitis associated with inflammatory changes in the ependyma and choroid plexuses that in his textbook he says, "the only known cause of hydrocephalus is meningitis."

Spiller and Allen,[10] in their report of two cases dealing with the causes of hydrocephalus, refer to Anton's support of Baginsky's opinion that acute hydrocephalus is identical with a nontuberculous inflammation involving not only the choroid plexuses, but also the walls and ependymal lining of the ventricles. Anton and Bonninghaus appear to be in accord with the opinion held by Gowers and others that these inflammatory changes are always associated with a simple or purulent meningitis.

Quincke[11] presents in detail the clinical studies of a number of cases in his effort to reach a definite understanding of the condition. Of the latter group of ten cases, two were examined post mortem, while in the others recovery, more or less complete, took place so that the clinical diagnoses could not be confirmed. In those cases which came to necropsy, no mention was made of the aqueduct of Sylvius. Beside the recognized causes of serous meningitis, Quincke points out the possibility of acute angioneurotic exudation from the choroid glands and ependyma, without fever or inflammation, a condition analogous to angioneurotic edema of the skin, and which he has designated angioneurotic hydrocephalus.

In summing up his conclusions regarding the pathologic changes in a number of cases of marked hydrocephalus in the adult, Parkes-Weber[12] says that "apparent thickening or slight granulation of the ependyma should not be accepted as evidence of a genuine inflammatory process." Continuing, he recalls that "the whole ependyma has been subjected to chronic stretching and the pressure exerted by the effusion must of necessity damage the tissues immediately bordering it, and will probably cause a necrosis of individual cells, and, in chronic cases, a reactive change will follow and will be accompanied by a certain amount of cell infiltration, as it is wherever a local necrosis occurs." Parkes-Weber believes that Quincke's theory of the purely angioneurotic origin of some cases of hydrocephalus "lacks evidence to support it," but he advances the idea of extravasation into the brain cavities, comparing such collections of fluid to the serous effusions into the pleural and peritoneal cavities resulting from a serous pleuritis or peritonitis.

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[9] Gowers: Diseases of the Nervous System.

[10] Spiller and Allen: Med. Bull. Univ. Penn., 1907, p. 108.

[11] Quincke: Samml. klin. Vortr., inn. Med., 1893, No. 23; ibid., Deutsch. Ztschr. f. Nervenh., 1897, **9**, 150.

[12] Parkes-Weber: Brain, 1902, **25**.

He explains the occurrence of idiopathic hydrocephalus as due in all probability to localized meningeal or ependymal inflammation producing an increase of cerebrospinal fluid. As an illustration of such localized inflammation, Parkes-Weber directs attention to the frequency, in fatal cases, of involvement of the posterior part of the roof of the fourth ventricle, and points out that the increase of fluid is due, not only to closure by the inflammatory exudate of the foramina in this situation, but that this region is one of the sites of election for the localized inflammation which leads to hydrocephalus.

This view is substantiated by Joslin's[13] report of eight cases of hydrocephalus following meningitis which showed this selective preference for the roof of the fourth ventricle. In all of his cases the foramen of Magendie and the openings into the cisterna lateralis had been closed and the roof of the ventricle rendered impervious by the inflammatory exudate. No changes were observed in the choroid plexuses and microscopic examination showed no thickening about the blood vessels. In one case of the series, that of a boy 16 years old, the aqueduct was occluded by a cystic tumor about 13 mm. in diameter, and adherent at several points to the choroid plexus of the third ventricle.

That the fourth ventricle is peculiarly liable to become the seat of a lesion causing dilatation of the cerebral ventricles and widening of the aqueduct of Sylvius, is abundantly attested by other workers, and cases of this type presenting symptoms of cerebellar tumor have been reported by Bramwell,[14] Spiller,[15] Finkelberg[16] and Rhein.[17]

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[13] Joslin: Am. Jour. Med. Sc., 1900, **120,** 444.

[14] Bramwell: Brain, 1899, **22,** 66.

[15] Spiller. Am. Jour. Med. Sc., 1902, **124,** 44.

[16] Finkelberg: Deutsch. Ztschr. f. Nervenh., 1905, **29,** 135.

[17] Rhein, J. H. W.: Jour. Am. Med. Assn., 1908, **51,** 1933.

Rhein's case, which showed the presence of a cyst in each cerebellopontine angle, is of further interest on account of an associated syringomyelia extending from the second cervical to the eighth dorsal segment of the cord. In the article Rhein says that Hinsdale, in a collection from the literature of 150 cases of syringomyelia, found hydrocephalus in fifteen.

Guthrie[18] says, in this connection, that primary hydrocephalus is frequently associated with syringomyelia, hydromyelia, and various forms of spina bifida, and these conditions he regards as being dependent on some abnormality of development of the meninges. Guthrie, in agreement with others, looks on meningitis as the principal etiologic factor in the majority of cases both of congenital and acquired hydrocephalus, and in his report of eight cases showing occlusion of the aqueduct, ascribes six to the results of meningitis, while one was due to the obliterating effect of a glioma of the pons, and, in the eighth, pressure of two symmetrical tubercular nodules effectually closed the iter.

The literature contains the accounts of a relatively small number of investigated cases of occlusion of the aqueduct, and the infrequency of careful and intimate examination in such instances is very much in evidence. Thus Bourneville and Noir cite a case of hydrocephalus in a child in which the aqueduct was completely closed, but a microscopic examination was not made. Touche, Oppenheim and D. Astros, without giving any specific instance, say that hydrocephalus affecting the third and lateral ventricles will follow plugging of the aqueduct of Sylvius, and von Becterew has observed obliteration of the aqueduct in some cases of cerebral syphilis with symptoms of dementia paralytica, but he does not go more into detail.

On the other hand, a considerable number of cases has been recorded in which hydrocephalus has been caused by obliteration of the fourth ventricle by papillary new growths springing from the floor, the roof and choroid plexus of the ventricle, notably the reports of Slaymaker and Elias,[19] Jacobson[20] and Douty.[21]

Spiller[15] reports a case of hydrocephalus internus presenting symptoms of cerebellar tumor due to closure of the aqueduct of Sylvius by proliferation of neuroglia, and in the same article he attributes a case of unilateral distention to partial blocking of the foramen of Monro from extension of an inflammatory process in the neighborhood. In another case of hydrocephalus which came under the observation of Spiller and Allen,[10] there was found occlusion of the aqueduct probably due to congenital malformation. The second of this group also seemed to be due to congenital malformation and was reported as a case of intense hydrocephalus without occlusion of the aqueduct.

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[18] Guthrie: Practitioner, London, 1910, **53,** 47.

[19] Slaymaker and Elias: Arch. Int. Med., 1909, **3,** 289.

[20] Jacobson: Hilton's Lectures on Pain and Rest.

[21] Douty: Brain, 1885, **8.**

The absence, in many instances, of demonstrable signs of a previous postbasic meningitis and the frequent development of a central gliosis, as demonstrated in this collection, lead to the belief that some form of obliterative process of the aqueduct, not necessarily associated with meningitis, could be discovered if diligently sought. As already suggested, the presence in the cerebrospinal fluid of some toxic product of metabolism or the influence of some disturbed function of internal secretion may be the exciting cause of a general or localized ependymitis leading, eventually, to closure of the aqueduct.

Thomas,[22] in his experimental work, has shown that hydrocephalus can be produced by injection into the ventricles of an irritating substance, and, using for the purpose a suspension of aleuronat, he has demonstrated that, through the acute inflammatory reaction which follows, obstruction may occur at the foramen of Monro, the foramen of Magendie, or in the aqueduct of Sylvius.

Accepting the well established facts regarding the origin and disposal of the ventricular fluid, it follows that, with plugging of the aqueduct, the essential cerebral avenues of escape are not sufficient to drain the ventricles and distention consequently results. With a definite obstruction to the normal flow through the aqueduct toward the fourth ventricle, facilities for the removal of cerebrospinal fluid are diminished, since the influence of the great cisterns and spinal subarachnoid cannot be brought to bear, thus throwing the burden of absorption on the cerebral sinuses and lymphatics.

REPORT OF CASES

CASE 1.—*History.*—L. T., who was admitted to the Beth Israel Hospital, March 29, 1911, and who died the day following an exploratory operation, was a boy 3½ years old, the second of three children. Of the other children the eldest was living and apparently perfectly normal at the age of 9 years; the youngest was born dead after an instrumental delivery.

The patient, who had never been seriously ill, was born, the mother stated, with a large head, but that up to nine months prior to his death the child seemed to be perfectly normal in every other respect, exhibiting at all times good mentality. Nine months before his admission to the hospital the patient had a fall, striking on the head; this fall did not cause any external injury, but unconsciousness for some minutes' duration ensued, and this was quickly followed by vomiting. Six weeks later a well-defined and typical attack of epilepsy developed, and thereafter the child complained much of headache and suffered repeated attacks of convulsions, with unconsciousness. The last convulsive seizure occurred four months before his admission to the hospital; at that time and five months after his head injury, the child's mother noticed that his gait had become slow and uncertain and it soon became impossible for him to stand or walk without assistance. Vomiting which had no relation to the ingestion of food, increased in frequency and the boy became ill-tempered, execessively irritable and nervous. His mentality, however, remained clear.

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[22] Thomas: Jour. Exper. Med., 1914, **19.**

Physical Examination.—The physical examination by Dr. Sachs showed that the patient was very well nourished, so much so, that the general and abundant distribution of fat suggested the possibility of some disturbance of the hypophysis.

The abdominal and thoracic organs showed no abnormalities. Neurologic examination demonstrated a spastic-ataxic gait, but there was no ataxia of the upper extremities and the Romberg sign was absent. The knee jerks were equal and not disturbed, but ankle clonus and the Babinsky reflex were present on both sides. Apparently there were no sensory disturbances. Examination of the cranial nerves showed double choked disk, with the left more swollen than the right; the retinal vessels were tortuous but there were no hemorrhages. Slight nystagmus appeared when the eyes were directed toward the right, but otherwise the movements of the eyeballs were not affected.

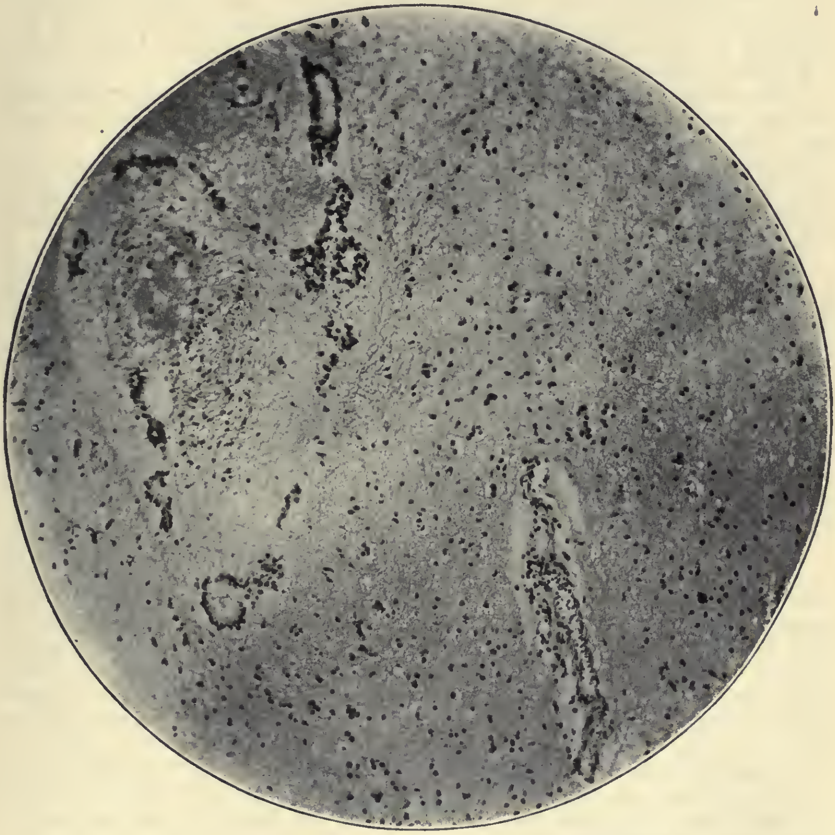

Fig. 1 (Case 1).—Showing central gliosis occluding the aqueduct of Sylvius, with proliferating ependymal cells arranging themselves in alveolar formation.

The pupillary reactions were not recorded.

Vision and hearing appeared to be normal in response to the usual tests. There was no deviation of the tongue when protruded, and the act of swallowing was performed perfectly. The sense of smell was not tested and the other cranial nerves showed nothing pathologic.

In the right parietal region a small angioma was exposed when the scalp was prepared for operation. In its greatest circumference the head measured 62 cm., the fontanels were closed and the frontal eminences were unusually prominent. The veins of the forehead were much distended.

Operation.—Decompression was performed by Dr. Sachs April 15, and the following day the patient died.

Gross and Microscopic Examination.—The gross specimens of the case submitted for examination were cut through the crura and complete occlusion of the aqueduct clearly shown.

Microscopic section made through the pons confirmed the macroscopic appearance and demonstrated the existence of a central gliosis, with a marked proliferation of ependymal cells, which in places near the central lesion showed a glandular arrangement tending to the formation of cysts.

In the subependymal glia tissue fibrils were present to a considerable depth and the same process could be observed extending ventrically along the raphé, and in this portion cellular elements were also abundant.

Examination of a portion of the cerebral cortex presented evidence of a general ependymitis, and section through the cortex, including a portion of the ependymal lining on one lateral ventricle, showed the existence of small nodules in which cell elements predominated.

The meninges showed no inflammatory process and no abnormality of the hypophysis could be made out. From these changes it is to be inferred that closure of the aqueduct of Sylvius had existed from the earliest period of development of the child's brain, and the fall sustained may perhaps be considered as an exciting cause of an ensuing ependymitis with consequent increase of the cerebrospinal fluid.

Case 2.—*History.*—To Dr. John Howland, in whose service at Bellevue Hospital this case occurred, and to Dr. Charles Norris, pathologist, acknowledgment is made for the clinical history, the necropsy report and the pathologic specimens in the case of G. N., a boy, 5½ months old, admitted to the hospital March 18, 1911, and who died March 27, 1911.

It was said by the mother of this baby that she had noticed no abnormality of development until, during the second month of his life, her attention was directed to the increasing size of the baby's head. Shortly after this the child began to have peculiar spasms lasting about three minutes, during which the upper and lower extremities became very stiff. These convulsive attacks recurred three or four times a day. Later, when the patient was about 4 months old, a lumbar puncture was made. The removal of a little more than a pint of cerebrospinal fluid brought about a marked improvement, which continued for six weeks, when the child again grew gradually worse and died March 27, 1911.

The patient, who was the only child, was delivered at term with the aid of instruments, after an active labor of twenty hours' duration. The parents of this child were living and well and there was no family history pointing to any possible etiologic influence.

Physical Examination.—Physical Examination showed an abnormally developed, but fairly well-nourished infant with a high, protruding forehead, prominent parietal bosses, large open fontanels and the whole vertex soft and pulsating.

Measurements of the head were as follows:

	Cm.
Greatest circumference	63
Occipito-mental circumference	61
Diameters:	
Occipito-frontal	22
Occipito-mental	21
Biparietal	17
Bitemporal	13.5
Suboccipito-bregmatic	18
Frontal-mental	18

Chest measurements, at full expansion at the level of the nipples, 39 cm.; at the costal margin, 41 cm. Abdomen, at the level of the umbilicus, 37 cm.; length of body, 68 cm.

The skin was rather mottled in appearance and showed a few erythematous areas. Examination of the thoracic and abdominal organs was negative.

On admission to the hospital the temperature was 99.6 F. and remained practically normal until the end; the day before death occurred the temperature fell to 94.8 and then rose again to normal. The limbs were somewhat spastic and the knee jerks were exaggerated.

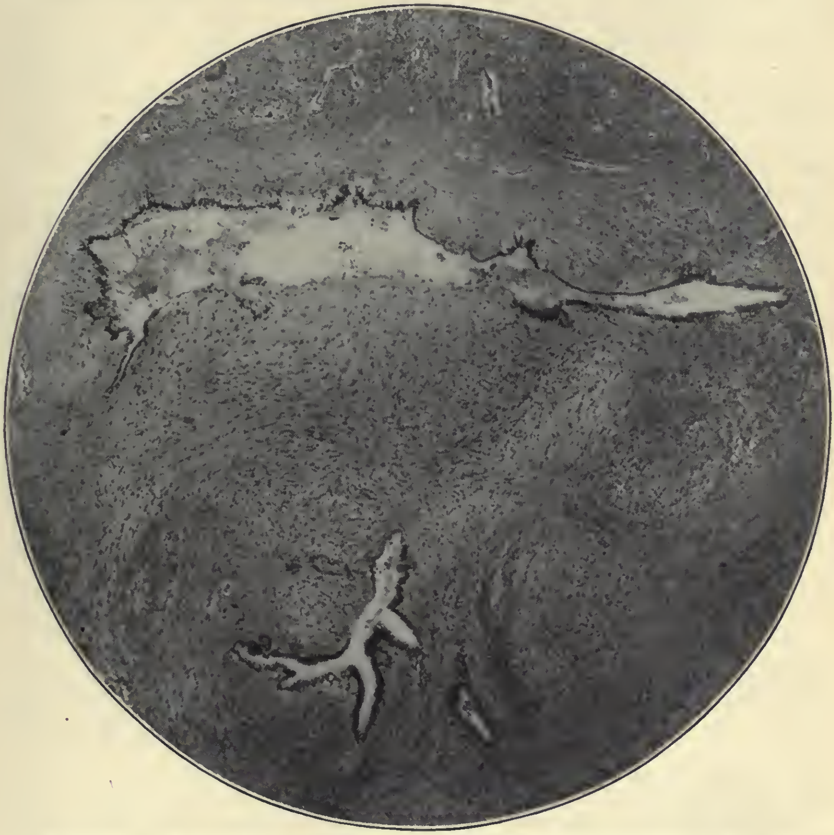

Fig 2 (Case 2).—Lesion of central gray matter showing closure of the aqueduct through a distinct proliferation of glia cells, giving to the new formation the appearance of a glioma.

Necropsy.—The necropsy confirmed the head measurements taken before death, and, in addition, records the dimensions of the anterior fontanel as 17 cm. in length; 15 cm. in its greatest width. The right parietal bone was considerably ossified and more prominent than the left. The tissues of the scalp were thin through distention, and, on removal of the cranial bones, the brain was revealed as a large sac filled with a clear fluid.

The cerebral cortex measuring 1 mm. in thickness was entirely without fissures or convolutions. The basilar ganglia appeared normal, the caudate nucleus on each side being especially well formed. The olfactory lobes and optic tracts were remarkably flattened and the hypophysis cerebri appeared softened.

The cerebellum, the medulla and the nerves at the base of the brain showed no abnormalities and the vessels in these regions were normal, while evidences of meningitis were absent.

Microscopic Examination.—Sections made through the midbrain showed complete occlusion of the aqueduct of Sylvius and microscopically the obliteration was seen to have been brought about by proliferation of glia cells, which, with a great increase of glia fibrils, had practically erased the contour of the central gray matter, producing the appearance of a glioma. The disposition of the ependyma cells to arrange themselves in the form of cysts was pronounced.

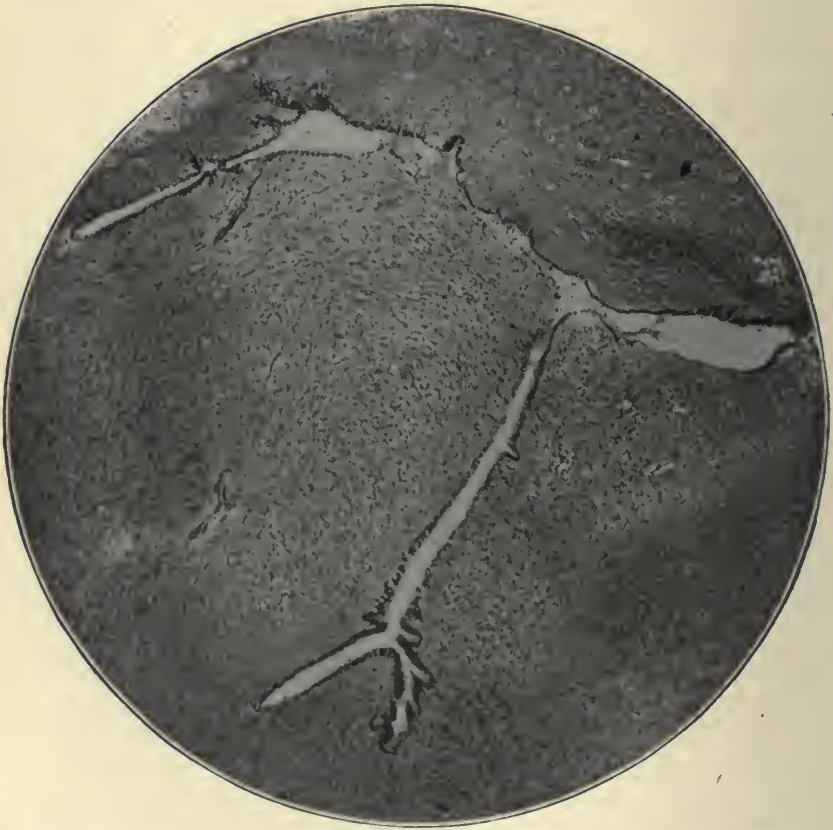

Fig. 3 (Case 2).—Another section of central gray matter showing obstruction by the new formation.

Above the point of obstruction the aqueduct became patent and appeared much wider than under normal conditions, and sacculated, while the immediately subjacent structures had been invaded by the same process.

The meninges appeared normal and the choroid plexuses presented no demonstrable changes.

Case 3.—*History.*—This patient, a girl, 2½ years old, was admitted to the children's ward at Bellevue Hospital, March 28, 1905, with the statement of the mother that the child was born with a very large head and that the condition had been gradually increasing. Of the family history little was learned beyond the fact that the parents were living and well, and that of several brothers and sisters all were perfectly normal.

Physical Examination.—It appeared that the child took its nourishment without any trouble, but had never been able to move her arms or legs. At the hospital it was found that, aside from complete paralysis of the extremities, the child, as far as could be determined, reacted to painful sensory stimuli by crying. The child was blind and did not seem to hear, but all the movements of the face were carried out in perfect coordination as observed when the patient cried, or at times seemed to smile. This showed that coordinated movements of the facial muscles were possible through emotional stimulation.

In posture this patient lay with the head fully extended, pressure at the point of contact between the back and occiput causing an erosion of the skin. The eyes could not be closed on account of the tension of the skin which drew the eyelids upward. Any movements of the patient's head or extremities caused her great distress.

The temperature of the patient was normal until two weeks before death, when it reached an elevation of 103 F., and during the last week of her life it remained above 101, dropping at the last to 97.

The extremities were spastic, legs and feet extended; the arms were flexed at the elbows and fingers folded in on the palms. In the upper extremities marked tremor was present. The tendon reflexes were very active.

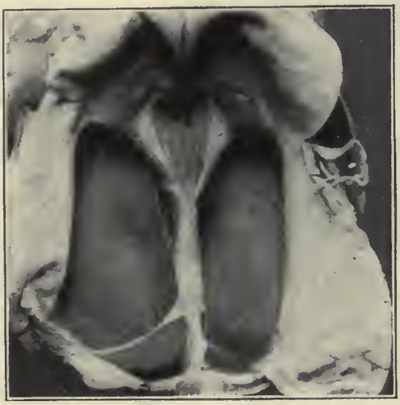

Fig. 4 (Case 3).—Gross specimen showing greatly distended third and lateral ventricles, with thin cerebral cortex. The basal ganglia and entrance to the aqueduct are clearly pictured.

The pupils were moderately dilated, equal and insensitive to light. There were no ocular paralyses. There was some rigidity of the abdominal muscles, but otherwise examination of the thoracic and abdominal organs was negative.

Necropsy.—Necropsy was performed May 10 by Dr. Charles Norris, and to him acknowledgment is made for the pathologic material. In general, the postmortem examination showed no special deviations from the normal, the findings being negative except for the presence in the posterior portions of the lower lobes of both lungs of hypostatic congestion and a cystic condition of the left suprarenal gland.

Head: Parietal, frontal and occipital bones were found to be about the thickness of heavy parchment. The measurements were as follows:

Posterior fontanel, small but open.

Anterior fontanel, along the coronal suture	22 cm.
In direction of sagittal suture	7 cm.

Lamboid suture, closed.

Measurements of face:

Chin to nasion	10 cm.
Malar to malar	9 cm.

In its greatest circumference the head measured, over the parietal and occipital protuberances, 67 cm., and the greatest anteroposterior diameter from the nasion to the external occipital protuberance was 52 cm.

On opening the calvarium the dura was found to be adherent, thin and translucent. There was no distinct evidence of pacchyonian granulations, and the superior longitudinal sinus was entirely empty.

After carefully removing the dura, the cortex appeared smooth and bloodless, with no suggestion of fissures or convolutions. The posterior third of both hemispheres consisted of a very thin, transparent membrane through which could be seen the large cavities of the distended lateral ventricles. The cortex of the anterior two thirds of both hemispheres was very thin, measuring 2 mm. in thickness, but gradually increasing toward the base of the brain where it passes over the lenticular nuclei. Here the cortex measured from 5 mm. to 1 cm. in thickness.

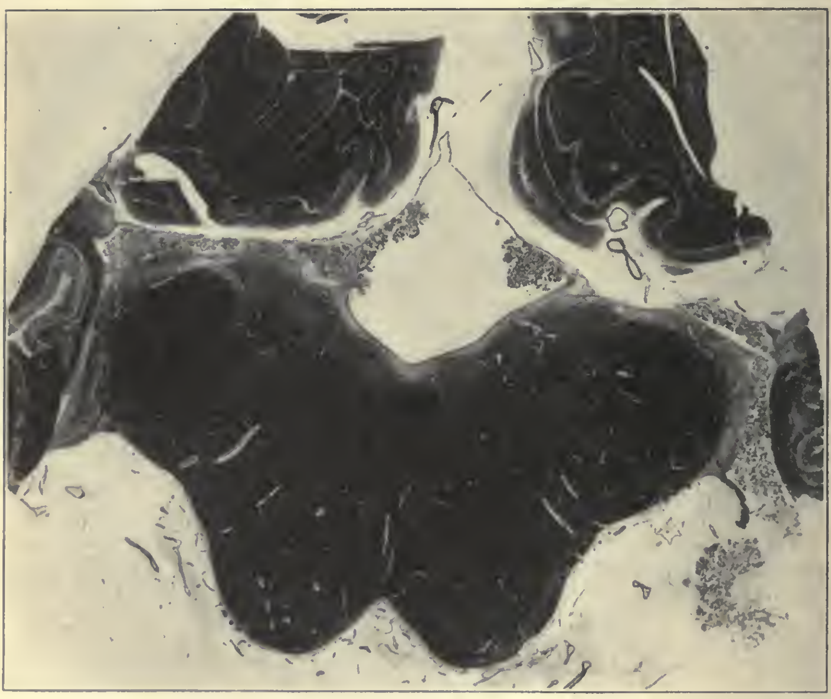

Fig. 5 (Case 3).—Cross section of medulla showing open fourth ventricle, entire absence of the pyramids, and choroid plexus unaffected.

The lateral ventricles were opened dorsally, liberating about 5 liters (estimated) of a clear, light-colored fluid. The corpus callosum was missing.

The basilar ganglia were present, though somewhat diminished in size. Lying between the optic thalami, the third ventricle appeared as a depression, and leading from its anterior portion the distended infundibulum could be made out, surrounded only by a thin membrane with the normal nervous tissue missing.

From the posterior portion of the third ventricle there might be seen the entrance to the aqueduct of Sylvius which later sectioning showed to be completely occluded. The fourth ventricle was not distended.

The optic nerves were smaller than normal, but were not compressed as were the olfactory lobes and olfactory tracts; all of the other cranial nerves appeared to be somewhat small, but otherwise showed nothing pathologic. The crura and pons from the ventral surface appeared normal, while the medulla and spinal cord showed plainly the entire absence of the pyramidal tracts. The cerebellum and peduncles were normal. The accompanying photographs (Figs. 4, 5 and 6) clearly demonstrate the absence of the pyramidal tracts, and this explains at once the complete paralysis of the extremities. But how are we to account for the coordinated movements of the facial muscles, the motor neurons being absent?

It is well known that, as we trace the phylogenetic development of the central nervous system from the lower to the higher forms of animal life, the function of motion is transferred from the basal ganglia to the cerebral cortex. If, for instance, the motor cortex of a dog or cat be destroyed, it will be found that these animals, after the shock of the operation has subsided, are still capable of walking, although in a disturbed manner, showing that some center other than the motor center in the cerebral cortex still has an influence over movements of the extremities. This center is undoubtedly situated somewhere in the basal ganglia.

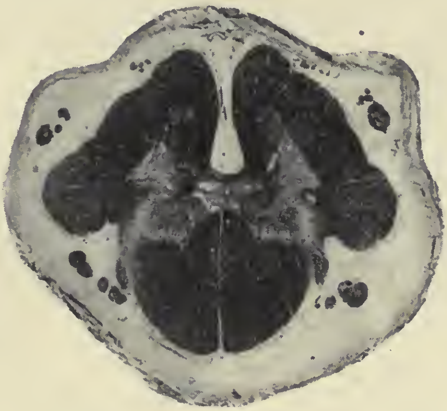

Fig. 6 (Case 3).—Section of spinal cord in the dorsal region showing again that the motor tracts are missing. The gray matter is normal.

Removal or destruction of the motor cortex of the human brain or brain of the higher monkeys, however, results in complete paralysis of the extremities, a fact which shows that the motor function has been completelty transferred from the basal ganglia to the cerebral cortex. It seems, however, that this transfer of the motor function has as yet not taken place completely in movements of the face, and particularly has it not taken in those muscular actions expressing the emotions; so we must conclude that the emotional movements of the face are still, to a certain extent, vested in the phylogenetic earlier motor centers of the basal ganglia. This conclusion is amply justified by the total absence, in Case 3, of a cerebral motor cortex.

Histologically, the essential features of gliosis are present in the pathologic changes which closed the aqueduct in this case, and while the process does not appear to be as active and aggressive as in the preceding pictures, occlusion is complete. Above the lesion the aqueduct is much dilated and the ependymal lining is normal. Sections show clearly the absence of the pyramidal tracts at all levels of the cerebrospinal axis.

The meninges did not show the presence of any inflammatory exudate and there were no appreciable changes in the choroid plexuses.

CASE 4.—*History.*—This child was admitted to the Presbyterian Hospital, Oct. 20, 1909, at the age of 6 months, and came immediately under the observation of Dr. John A. Hartwell, whose interest eventually made possible a histologic study of this case.

According to the records of the hospital, the child was born normally at full term, of perfectly healthy parents. Of the other children in the family, two brothers were living and well at the ages of 12 and 9 years, respectively; each of two sisters died within one hour after birth, the delivery in each case having been instrumental.

This baby nursed up to the time of her admission to the hospital. When 6 weeks old, however, she suffered from serious bowel trouble, a condition which was described by the family physician as marasmus. The illness continued about six weeks and the child had "weak spells"—"internal convulsions," the mother called them—when she seemed dazed and almost unconscious for a whole day at a time. At the age of 3 months the child had a well-defined convulsion, lasting about five minutes; this was the only pronounced epileptiform attack which occurred, and was caused, the physician believed, by a condition of chronic constipation which required the daily use of a cathartic.

The mother stated that the child's head had been large since birth and to her had never seemed like other children. She had never attempted to raise the head, and one eye had turned outward from birth. The baby's eyesight during the last month had been very poor, and the mother believed that the baby could not see at all, but lately she had appeared to recognize her mother's voice. During the previous six weeks the head had grown considerably in size.

Physical Examination (by Dr. Davis).—The patient was a moderately well-nourished child with an enlarged, square head.

Measurements:

	Inches
Occipito-frontal	19½
Occipito-bregmatic	18¾
Occipito-mental	19¾
Fronto-mental	19¾
Mastoid to mastoid over the head	15½

The anterior fontanel was open and its anteroposterior diameter and the lateral diameter each measured 4 inches. The parietofrontal sutures had not yet united and there was no pulsation.

Eyes, ears, nose, mouth and face were of normal size. There were no glandular enlargements to be made out. Examination of the thoracic and abdominal organs was negative. The knee jerks were exaggerated and there was ankle clonus and the Babinsky reflex on both sides.

Operation and Course.—Oct. 22, 1909, an operation was undertaken by Dr. Hartwell for the purpose of draining the ventricles of the brain into the peritoneal cavity.

Procedure: Three incisions were made: first, in the right side of the abdomen and through the peritoneum, about two inches below the costal margin; second, over the middle of the right clavicle; third, 1 inch above and behind the right external auditory meatus. A probe was then passed upward subcutaneously from the abdominal incision to the clavicular incision. A grooved director was passed from this latter opening to the wound in the scalp, making a channel for the probe. A heavy silk thread was then drawn through these tracks, making a subcutaneous channel from the skull to the abdomen. A double twisted wire was then made to replace the silk. The dura was incised through a quarter-inch trephine opening in the skull and the end of the loop of wire was driven by means of a probe into the brain in the direction of the opposite external meatus. The lower end of the wire, formed into a loop, was passed into the peritoneal cavity and the three wounds closed.

A considerable amount of cerebrospinal fluid was lost at the time of the operation, but the patient's condition was satisfactory, and on October 30 she left the hospital improved.

The temperature following the operation ran along at 102 F. or over, 104 being the highest temperature recorded. On the sixth day the temperature began to fall and then remained below 100. The pulse varied from 140 to 200 per minute and slowed finally to 110 to 100; respirations from 40 to 30. On the fifth day following the operation the sutures were removed and the wounds were found to be clear. In spite of the rapid pulse it always maintained fair quality. The patient had numerous muscular twitchings bilaterally for several days, but these gradually lessened and finally disappeared. The fontanels became very much depressed, showing that drainage from the ventricles was actively taking place.

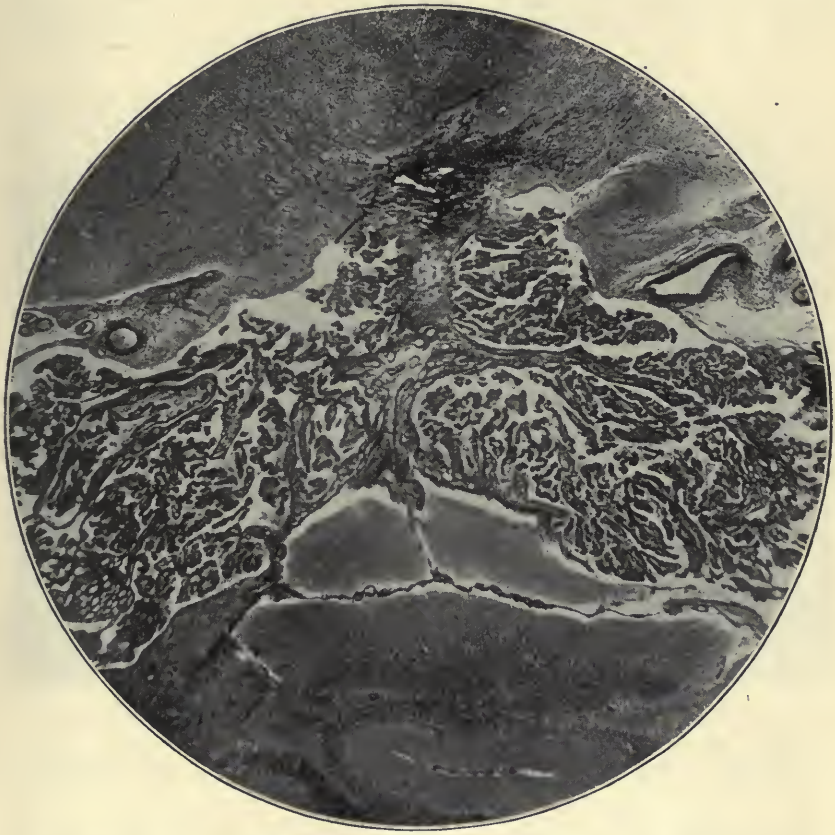

Fig. 7 (Case 4).—Section taken at the beginning of the fourth ventricle, showing the first appearance of the obliterating process as a pedunculated mass composed of proliferating choroidal cells. Except near the choroid plexus, it shows no special disturbance.

The child remained with the parents until Jan. 4, 1911, when she was admitted to Bellevue Hospital suffering with mastoiditis complicating her hydrocephalus, which had not greatly improved during the interval. The baby's general condition was good and the neurologic examination gave about the same results as at first observed. The fontanels were closed. There was slight internal strabismus, and while the pupils reacted sluggishly to light, it was evident that the child was blind.

The mastoid condition was relieved by operation, and at the same time Dr. Hartwell removed the silver wire which, in the first instance, had been introduced for purposes of drainage of cerebrospinal fluid. It was found that the subcutaneous channel was completely lined by epithelium and permanent drainage into the peritoneal cavity established. Improvement was manifest for a time after these aspirations, but death occurred in her own home a few weeks later.

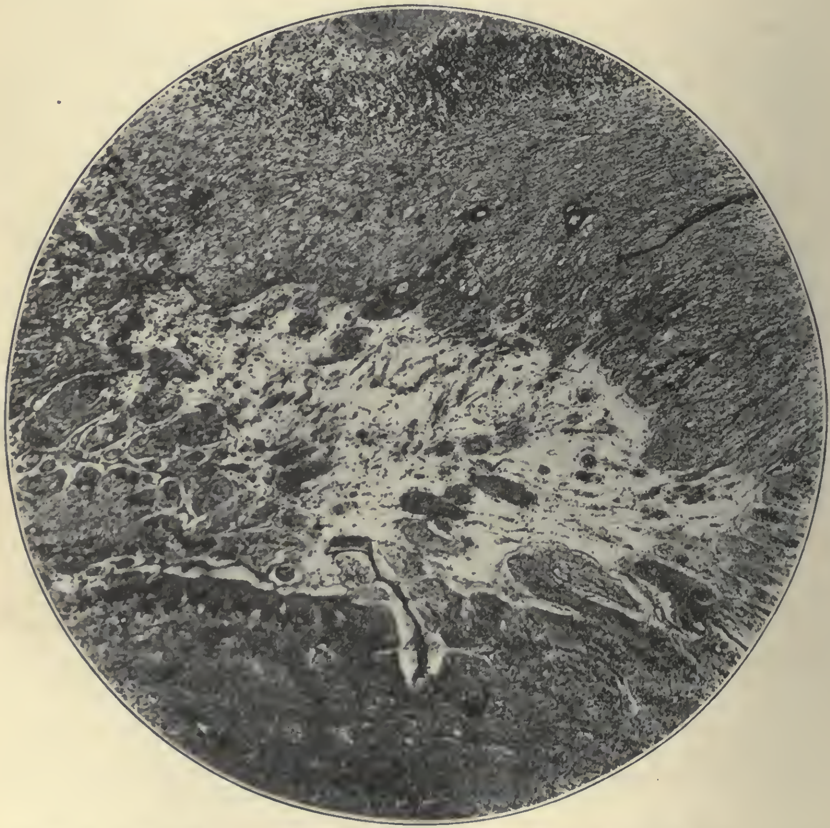

Fig. 8 (Case 4).—Section greatly enlarged, showing at the level of the eighth cranial nerve invasion of the pons and cerebellum by the proliferating new growth, causing complete occlusion of the ventricle.

Microscopic Examination.—This shows complete obliteration of the fourth ventricle and the aqueduct of Sylvius.

In Figure 7 may be seen the process beginning in the raphé of the floor of the ventricle, appearing as a pedunculated tumor mass composed of choroidal cells, with invasion of both the cerebellum and medulla. Passing cephalically, these choroidal cells increased in quantity, and in Figure 8, at the level of the nucleus of the eighth cranial nerve, the ventricle appears to be completely filled.

Here as at other levels proliferating choroidal cells invade the nerve tissue of the cerebellum, medulla and pons in typical neoplastic fashion.

The aqueduct of Sylvius throughout its course is entirely closed, not by choroidal cells, but by proliferation of the surrounding glia cells.

At those points where the cerebellum and medulla have been invaded, choroidal cells, having taken on the characteristics of ependymal cells, have arranged themselves in the form of small cysts.

The choroidal cells are unquestionably spongioblastic, derived from the same mother cell, which gives origin to the glia and ependymal cell.

Case 5.—*History.*—The only clinical history obtainable in this case is taken from the records of the City Hospital and from the nurses' bedside notes, and relates principally to the surgical treatment which this child of 15 months received from the time of his admission to the ward, Feb. 11, 1911, to the date of his death, Oct. 26, 1911.

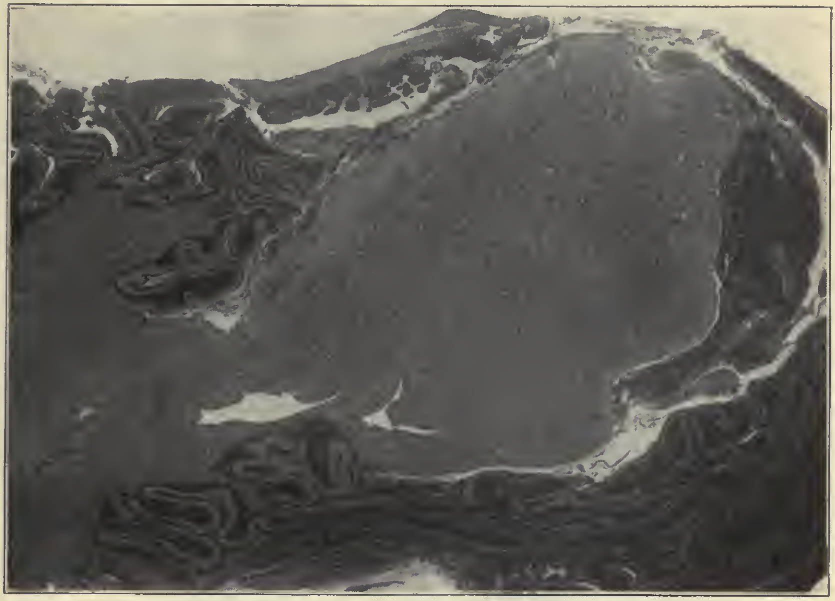

Fig. 9 (Case 5).—Cross section in the region of the nucleus of the third cranial nerve showing presence of small tumor mass, histologically a glioma, proceeding from the floor of the sylvian aqueduct and partly occluding the lumen.

The specimens of this and the following case were furnished by Dr. John H. Larkin, pathologist to the Department of Charities, New York City.

The case is that of a boy, 1 year and 3 months old, who showed on physical examination a large head, globular in form, with greatly enlarged fontanels, through which fluctuation could be plainly felt. The face was small and pinched in appearance, eyes prominent and bulging, and the superficial veins of the head distended.

Dr. Dawbarn, in whose service at the City Hospital the case occurred, attempted to drain the lateral ventricles into Stenson's duct, and with this end in view an operation was performed by him, Sept. 25, 1911.

Operation and Course.—The records state that a large semicurved needle was introduced into the anterior fontanel well away from the middle line and made to merge from the anterior part of the parotid gland. A No. 18 silk tape was then carried through, cut off at each end even with the surface, and the ends buried by closing both incisions.

The greatest circumference of the head before operation was 67.5 cm. After operation, which was attended by a considerable loss of cerebrospinal fluid, measurement of the head showed a circumference of 65 cm., and by September 30 this was further reduced to 63.7 cm.

During the month of August it appears that the baby had four severe convulsions of from five to seven minutes' duration, and again on September 24, the day before the operation, a very severe convulsion occurred; and on September 25, shortly after the operation, there is a history of repeated slight attacks. Vomiting and unusual restlessness then set in and continued for two days, when the child again became quiet and retained most of his nourishment. It was noticed on September 27 that the patient's body and extremities had become very stiff and vomiting occurred more frequently. During the whole of his stay at the hospital the baby was, at times, extremely restless and frequently cried throughout entire day and could not be pacified.

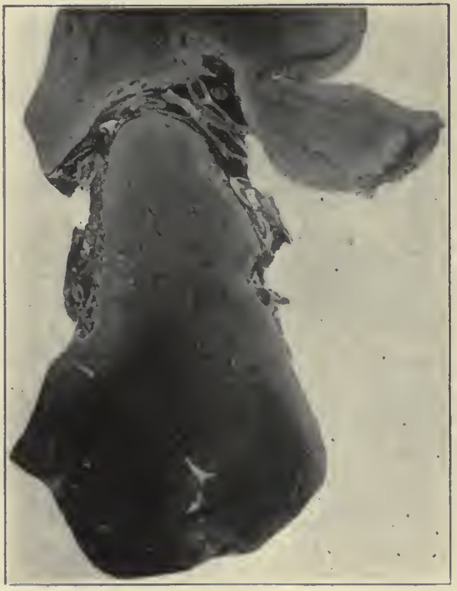

Fig. 10 (Case 5).—Transection through pons, again illustrating effect of a small glioma with active proliferation of glia cells at the base of the new growth. Changes in the subependymal structures and in the choroid plexus may be observed under high magnification.

Gradually increasing weakness and frequent periods of restlessness marked the progress of the succeeding days, and on October 9 a second operation similar to the first was performed on the opposite side of the head. During the three days following this operation the child seemed better and was making satisfactory progress, when a marked weakness supervened, and, although the patient took nourishment fairly well, this weakness increased and gradually it became more and more difficult to administer nourishment. Death finally took place Oct. 26, 1911.

Examination of Brain.—The gross specimen in this case was of unusual appearance, the bases of the anterior crura being almost unrecognizable as such. The right crus, very much enlarged, appeared as a tumor mass about 1.5 cm. long and 2 cm. in its transverse diameter; the left crus was smaller, measuring about 1 cm. in thickness.

These masses disappear at a point where the crura pass into the pons; cephalically, they extend to a point considerably above the red nuclei. Between these two masses the neutral fissure reaches between the red nuclei to the level of the aqueduct.

The aqueduct in the region of the nucleus of the third cranial nerve appears to be entirely closed, but microscopically a minute sacculated opening remains, and this is partly filled with a small tumor formation growing in from the roof of the aqueduct; similarly, at a point where the aqueduct normally tends to widen out centrally, another small growth makes its appearance, invading the lumen of the aqueduct from above. At this same level a very small new formation may be seen taking origin from the subependymal structures of the floor of the aqueduct.

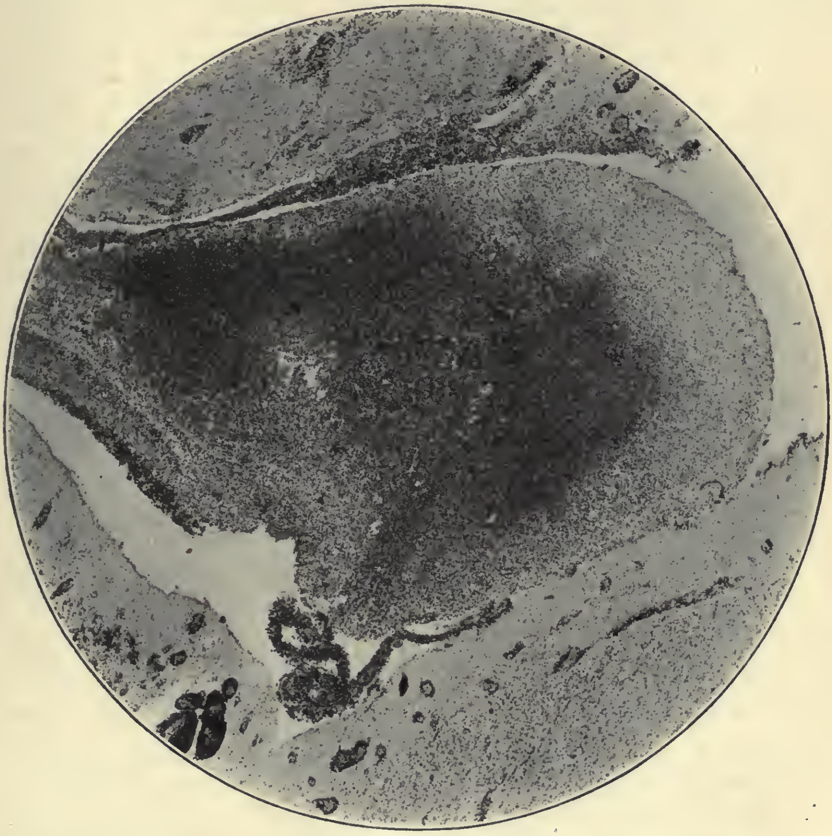

Fig. 11 (Case 6).—Syphilitic gumma proceeding from the pia-arachnoid, invading and partially occluding the fourth ventricle. Characteristic changes in the lymph and blood vessels are much in evidence.

Microscopic Examination.—Histologically, these invading masses are gliomata. The choroid plexuses do not appear to be the seat of inflammatory changes, but many choroidal vessels are engorged, indicating a lesion of obstructive type interfering with the normal functioning of these glands.

The general ependyma shows no abnormality, but in the more deeply lying tissues there is very evident abnormal cell activity, with extensive perivascular round cell infiltration. Here several contributory factors in the production of hydrocephalus may be seen in combination. Not only is the aqueduct encroached on by protrusion into its lumen of various small gliomata, but the processes of secretion and absorption have been disturbed through involvement of the choroidal vessels and ventricular walls.

Case 6.—*History.*—As in the preceding case, the hospital records are incomplete, the available history dealing chiefly with incidents of the child's birth. The baby was born at full term of a young multipara, who, as far as could be learned, was a perfectly normal individual. Her other children were born normally, and they made entirely satisfactory progress through infancy and childhood. In this instance, however, labor was prolonged and difficult, the second stage lasting thirty-six hours, and it was only after craniotomy had been performed that delivery could be accomplished. The mother made a good recovery and returned the next year to the maternity wards of the City Hospital, where she gave birth to a perfectly normal child.

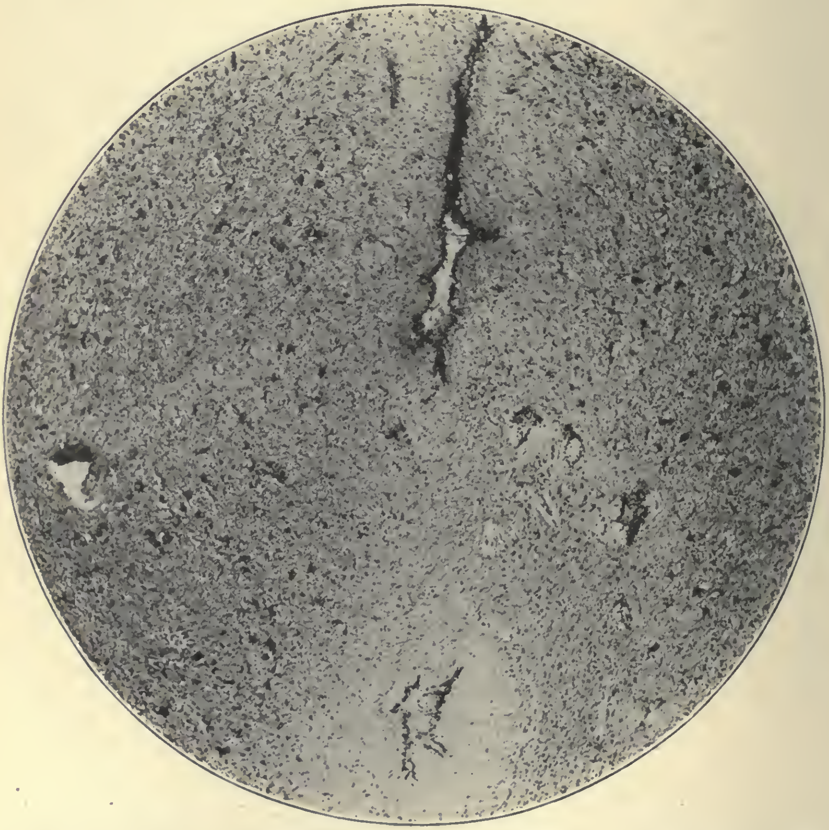

Fig. 12 (Case 6).—The region of the nucleus of the third cranial nerve, showing complete occlusion of the aqueduct and activity of the ependymal and perivascular changes in the subependymal tissue.

While nothing was discovered in the history on the part of the mother to suggest a possible cause of the hydrocephalus, the fetal brain was examined by the Noguchi method and *Spirochaeta pallida* were found in the cerebral tissue. This placed the origin of this case definitely on a syphilitic basis, and is the only one of the series to react in this manner.

Further microscopic evidence of the syphilitic nature of this lesion is to be found in high-power study of the sections.

Examination of Brain.—The gross specimens showed fairly well-developed pons and medulla, while the basal ganglia were of fair size and consistency. The cerebral cortex, however, was thinned out to a mere sac-like formation, containing very little brain substance and possessing no convolutions or fissures.

Microscopic Examination.—Microscopically, the picture is that of meningo-encephalitis with characteristic blood-vessel changes in which the perivascular lymph spaces are crowded with infiltrated round cells and lymphocytes. The aqueduct in the sections is completetly closed and considerable cell activity is to be made out in the ependyma and periependymal tissues.

Many small spaces lined by cuboidal cells give the appearance of cysts, suggesting the tendency of certain modified ependymal cells under stimulation to arrange themselves in this manner, but undoubtedly these stand in relation to obliterated vessels remaining as evidence of earlier lymph stasis with consequent changes in adjacent areas.

In the region of the nucleus of the eighth cranial nerve a small gumma encroaches on the fourth ventricle, impeding the flow of cerebrospinal fluid. This pedunculated mass, originating in the pia-arachnoid, stands in close association with the choroid plexus of the fourth ventricle, and while the plexus and the choroidal cells themselves show no changes, the inflammatory exudate extends laterally, following for a considerable distance the pia covering of the gland. The exudate itself, marked by the presence of many lymphocytes and polynuclear leukocytes and showing areas of necrosis, is the seat of an active as well as a chronic inflammation.

Case 7.—*History.*—To Dr. Elise L'Esperance, pathologist to the New York Women's Infirmary and assistant in pathology at the Cornell University Medical College, we are indebted for the specimens and history of this case.

The history shows that the parents of this child were young and healthy, and that the birth occurred as a miscarriage in the seventh month of pregnancy. The child lived about one hour.

Necropsy.—At the necropsy, performed by Dr. James Ewing, the head presented a high grade of hydrocephalus, with all the ventricles dilated. Measurements, however, were not taken.

The convolutions were flattened and the cerebral cortex measured from one-eighth to one-fourth of an inch in thickness. The lungs were completely collapsed and the heart on the right side was hypertrophied.

Both kidneys were cystic, the left atrophic, measuring 1.5 cm. by 1 cm.; the right hypertrophied, measuring 7 by 4 by 3.5 cm. There were cysts in the dilated renal tubules. The suprarenals were not affected; thyroid normal. The spleen and gastro-intestinal tract showed no abnormalities.

Microscopic Examination.—To the naked eye the aqueduct appears to be closed, but microscopically a passage remains in the shape of a minute slit, about which an active proliferative process may be made out, while at either end of the opening there is a well-advanced gliosis. Inflammatory and vascular changes have occurred in the choroid plexuses, with lymphocytic infiltration of the vessels of the medulla, pons and cerebral cortex.

Case 8.—*History.*—An infant, 7 months old at the time of her death, was born, so the mother declared, with a head of normal size, but labor was difficult and delivery was finally effected after the ordinary forceps operation.

On admission to the hospital, Oct. 9, 1913, the chief complaints, as entered in the clinical history, were abnormally large head, great weakness and listlessness.

During her earliest infancy the baby suffered from obstinate constipation, but otherwise was perfectly normal, and the increase in the size of the head was so gradual that the abnormality was not definitely recognized until, in the fifth month of life, a friend directed the mother's attention to the now apparent disproportionate size of the child's head.

The mother then placed the infant in the Babies' Hospital, where she remained under observation for a short time. It had been the mother's custom to return to the hospital daily for the purpose of nursing the baby, and on the occasion of her last visit she found the child in a weak and exhausted condition following a lumbar puncture, and against advice removed the patient to her own home. Later, on the same day, however, the mother applied for admission to Bellevue Hospital, where eventually the child came under the observation of Dr. John Hartwell, who later performed an operation for the relief of the hydrocephalus.

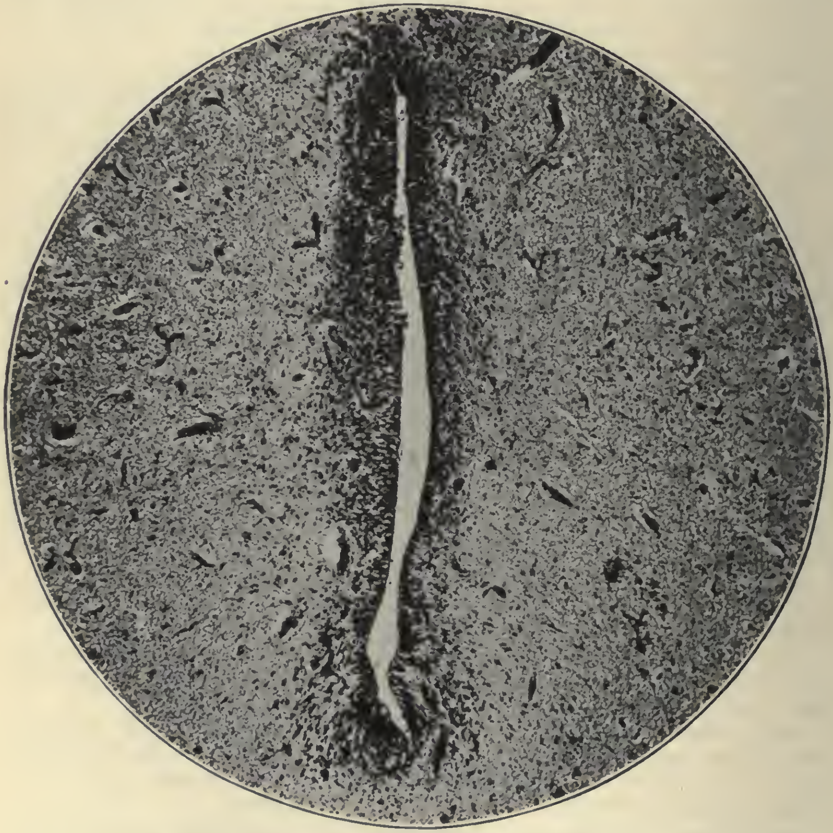

Fig. 13 (Case 7).—Showing, under high magnification, active gliosis taking place about embryologically defective structure.

In the family history it is perhaps significant that the Wassermann reaction in the blood of the mother was found to be positive, but this examination was made only after operation had been done.

The mother was in ordinary good health at this time and the father died a short time before of spinal meningitis. No definite venereal history was obtained. As a predisposing cause of the hydrocephalus the traumatic influence of an instrumental delivery may possibly be considered. The patient was the only child and the mother gave no history of abortion or miscarriage.

Physical Examination.—The appearance of the patient at the time of admission to the hospital was that of a hydrocephalic, female infant, well nourished, but very weak and listless. There was an abundant growth of hair.

The head in its greatest circumference measured 52 cm. The fontanels were open; the anterior, bulging and fluctuating, measured 16.5 cm. in its transverse diameter; the posterior was 3 cm. across.

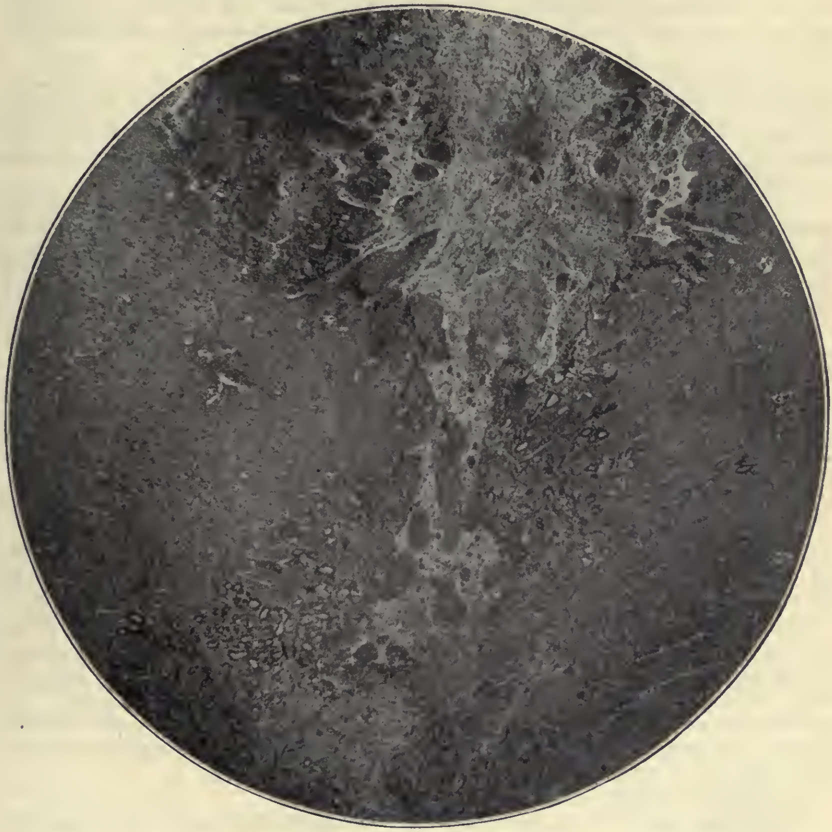

Fig. 14 (Case 8).—Section of medulla in the midolivary region of the fourth ventricle, showing complete obliteration by a central gliosis.

The eyes showed external strabismus, the defect being more marked in the right than in the left eye. The conjunctivae were blue and congested. Examination of the eyegrounds showed the absence of choked disk. The vessels were slightly congested but there were no hemorrhages or papilledema.

The nose, ears and tongue were normal. There was no rigidity of the muscles of the neck; the hands were flexed and thumbs adducted. There was no abnormality of the lower extremities except webbing between the second and third toes of the left foot. The knee jerks were somewhat exaggerated.

The heart, which showed poor muscle tone, was otherwise negative. The action was slow, regular, and there were no murmurs. The lungs were clear.

October 10 a lumbar puncture was made and 10 c.c. of a blood-tinged fluid withdrawn. The records do not show that a Wassermann test was made.

Operation.—October 22, Dr. John A. Hartwell performed an operation designed to drain the ventricles into the jugular vein. The proceeding was as follows:

A section of a vein 4 inches in length was taken from the mother's arm, and this was sutured, one end to the cardiac end of the external jugular vein of the patient, the other end carried by means of a cannula and sutured to the dura mater, the cannula itself being made to enter the lateral ventricle and the external jugular vein, which effectually drained the cerebral cavities.

A considerable amount of cerebrospinal fluid was lost during the operation, so that the fontanels, which previously had been hard and bulging, were, after the procedure, soft and flaccid, while the diameter of the head was reduced to 51 cm.

The fluid in the ventricles was confined under pressure, but the subarachnoid space appeared to be empty. The partial collapse of the skull was due in a measure to loss of cerebrospinal fluid during the operation, but this condition continued afterward, thus demonstrating the fact that drainage had been established and maintained.

The child's condition, however, was not more satisfactory than before the operation, and the weakness and depression, which had marked the case from the beginning, continued until death ensued the following day. The temperature of the patient continued practically normal during the whole period of observation.

Necropsy.—A full necropsy was refused by relatives, but the report as made by Dr. G. H. Wallace is as follows:

	Cm.
Greatest circumference of the head	51
From glabella to external occipital protuberance	33
Distance between mastoid processes	34
Anterior fontanel (depressed)	9 by 14
Posterior fontanel	1.5 by 1

A linear incision 4 inches in length extended downward parallel to the external carotid artery from a point 2 cm. above and 1 cm. posterior to the tip of the right mastoid, which was sutured and clean.

On opening the incision the right external jugular vein was found to be sutured to a transplanted vein which was attached to a cannula at its upper extremity, the cannula itself extending through the brain substance into the right lateral ventricle. The tissues of the scalp were otherwise normal. On opening the skull the dura was found to be adherent to the bone, the cerebral cortex was flattened and fissures and sulci were practically obliterated. In places the cortex was so thin as to be almost transparent.

The cranial nerves were softened and edematous.

The bridge of the nose was depressed and alae nasi flattened. The hair of the head was fine and abundant and extended over the forehead on each side to the supra-orbital ridge.

Macroscopically, the pathologic specimen revealed obliteration of the fourth ventricle by a tumor formation, and complete occlusion of the lower portion of the aqueduct of Sylvius, which showed marked dilatation in front of the posterior corpora quadrigemina. The dilated aqueduct opened into a greatly distended third ventricle, and the wall of the lateral ventricles was stretched to extreme thinness.

Structurally the lesion causing occlusion in this instance is practically identical with that of Dr. Hartwell's previous case, and the same invasion of surrounding tissues by choroidal cells is to be observed microscopically, but the cerebellum does not participate to the same extent as in Case 4.

The fourth ventricle and lower part of the aqueduct were involved in the obliterating process, and while the upper part of the aqueduct was open, active gliosis, with cell proliferation and fibril formation, was a marked feature.

The choroid plexuses did not show any demonstrable changes.

SUMMARY

Reviewing the facts as they appear from our own observations and from a survey of the literature, it seems not unreasonable to attribute many, if not the majority, of cases of the congenital form of this disease to closure of the aqueduct of Sylvius through proliferation of the glia and ependymal tissues, or to invasion of the fourth ventricle by tumors having their origin in the floor, the choroid plexus or the membranous roof of the ventricle.

Those cases, also, developing acutely in previously healthy adults and older children, and which have shown microscopically the same pathologic changes, may have been brought about in the same manner, namely, through the stimulation by some chemical poisoning of a tissue which is embryologically defective. These cases, no doubt, differ etiologically from that large group following meningitis, the acute infectious diseases and those due to bacterial invasion of the brain substance and ependyma from extension of suppurative processes of the middle ear or cells of the mastoid, frontal and ethmoid bones.

A consideration of the life processes of the cell offers an explanation of the occurrence of many cases of congenital and acquired closure of the sylvian aqueduct.

Metabolism is nowhere more delicately expressed than in the highly complex chemical reactions of the cells of the central nervous system; and while knowledge of these reactions is still far from complete, it is, nevertheless, conceivable that any slight noxious influence may be sufficient seriously to disturb the latent forces of the glia cells, resulting in the dominating influence of one or another of the processes residing in these cells. These life processes may be divided into the nutritive, the formative and the functional activities. In the first, which involves an appropriation of nutritive substances from the blood, potential energy is stored up and is subsequently translated into formative or functional activity, as represented by cell division, on the one hand, or by functionation of the specialized cell, on the other. In cells which have become highly specialized, as the nerve cell, gland cell and muscle cell, the potential energy of the cell body is converted into the predominating activity, and the formative process is held in abeyance, and, so long as the normal relation between synthesis and catalysis is maintained, functional activity of the cell remains in a state of constancy. On the other hand, in those cells not highly specialized, as the ependymal, glia and the connective tissue cells, formative activity is easily awakened, and so it happens that in many cases of hydrocephalus, stimulation of these cells by some irritating substance results in an active proliferative process which involves not only the ependyma but the subependymal tissues of the aqueduct of Sylvius, as seen in the obliterative glioses which figure conspicuously in the accompanying photographs.

The exact nature, source and means of access of such damaging stimuli are not always readily determined, and, barring the possible influence of syphilis and bacterial invasion of the meninges, ependyma and choroid plexuses, there remain to be studied more closely the causal effects of circulating toxic byproducts of fetal or maternal metabolism, and variation in function of the endocrine glands.

Syphilis has not operated as a known etiologic factor in this sequence, with the exception of Case 6, in which *Spirochaeta pallida* have been found in the cerebral tissue. The Levaditi method has failed to show the presence of spirochetes in two other cases (2 and 7) which it was thought might be explained on the ground of a luetic infection. The clinical records do not include reports of the Wassermann reaction in the blood or spinal fluids of the parents of these children.

A CONTRIBUTION TO THE DIAGNOSIS OF SPINAL CORD TUMORS IN CHILDHOOD *

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During the last fifty years, as a result of continuous study of the physiology and pathology of the spinal cord, the clinical diagnosis of intravertebral tumor has been made with increasing frequency. Many case reports are now available. From these it would appear that growths within the spine occur exceptionally in childhood, differing in this respect from those within the cranium. Stursberg[1] collected from the literature reports of 141 operations; one patient was under 10 years, and only six were between the ages of 10 and 15. Schultze,[2] in his series, introduced but one case, a girl of 4 years, while the age of the youngest in Nonne's[3] latest report of sixteen operations was 19 years. The occurrence of these tumors in early life was not noted in Flatau's[4] recent monograph.

Postmortem statistics differ from these very occasional findings in the clinic. Among 251 collected reports of tumors of the spinal cord, Schlesinger[5] found 33 (13 per cent.) in patients between the ages of 1 and 9 years, and 27 (11 per cent.) between the ages of 10 and 15. The earlier compilations of Gowers and Horsley[6] (10 per cent.) and Lloyd and Mills[7] (12 per cent.) show practically the same ratio.

The following case report is a contribution to the study and diagnosis of spinal cord tumors in childhood.

REPORT OF CASE

Clinical History.—A. L. (No. 8241, University of California Hospital), aged 1 year, 11 months, birthplace, San Francisco, was admitted Nov. 13, 1914; died Nov. 21, 1914. Under observation eight days.

Family History.—Negative; no tuberculosis, nervous disease or rheumatism; four other children, living and well.

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* From the Department of Pediatrics, University of California Medical School.

[1] Stursberg: Centralbl. f. d. Grenzgeb. d. Med. u. Chir, 1908, **11,** 91.

[2] Schultze, F.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1903, **12,** 153.

[3] Nonne: Deutsche. Ztschr. f. Nervenh., 1913, **47,** 436.

[4] Flatau: Wirbel-und Rückenmarksgeschwülste, in Lewandowsky's Handbuch der Neurologie, Ed. 1, Berlin, S. Karger, 1912, **2.**

[5] Schlesinger: Beitrag zur Klinik der Rückenmarks-und Wirbeltumoren, Vienna, 1898.

[6] Gowers and Horsley: Med.-Chir. Tr., London, 1888.

[7] Lloyd and Mills: Spinal Tumors, in Pepper's System of Practical Medicine, Ed. 1, Philadelphia, Lea, 1885-1886.

Past History.—Birthweight, 12 pounds; breast fed more than six months; began to walk and talk at the usual time. The first illness, measles, some eight months prior to admission, was not severe; there were no immediate after-effects.

Present Illness.—For four months the patient had been continuously ill. His sickness began when "he caught cold which settled in the glands of his neck and caused his head to lean a little to the right. Sometimes he had pain in the right shoulder." After fourteen days, the right hand was noticeably weak. According to a physician who saw him shortly afterward, it was practically useless. The patient had beside, at this time, a sore throat, much enlarged cervical glands, and a temperature of 100 F. After six weeks, weakness, which had since increased progressively, was noted in the right leg. Three months after the beginning of his illness the patient was confined to his bed. About this time the child cried a great deal, for about one week, with pain or itching in the right hand and left shoulder, which was relieved by rubbing. Soon his left hand became weak. Since one month, there had been intermittent fever with night sweats. Urination had been painful; there was retention at times; the bowels had been normal; the appetite, very good until recently. There had never been any cough, convulsions, vomiting or night cries. There had never been any severe pain. The mind had always been clear.

Physical Examination.—(Nov. 14 to 19, 1914). A well-developed, well-nourished baby, with a somewhat worried expression, mentally alert, lay perfectly quiet with his head inclined to the right. When disturbed, he rolled his head from side to side, crying "No! No!" in a good clear voice. He put out his tongue when asked. The neck, held stiff, was rigid, and although he could turn his head, he never raised it up. There was no rigidity of the lower spine. Pressure over the lower cervical vertebrae elicited pain, but this was not found elsewhere along the vertebrae. There was no kyphosis or scoliosis. Many discrete, enlarged cervical glands were apparent on both sides of the neck, but beneath the angle of the right jaw and under the right sternocleidomastoid there was a mass of glands that were noticeably enlarged and tender. Glands were also palpable in the axilla and inguinal regions. Both sides of the chest moved equally. Heart, lungs, and abdomen were negative. The temperature ranged from 38.2 to 39.8 C.; pulse 120 to 140; respirations 22 to 35. On repeated examination the urine was always negative. The leukocytes varied from 10,000 to 20,000, and the neutrophils from 44 per cent. to 88 per cent. The Wassermann test was negative in the blood serum. The von Pirquet test was strongly positive to both human and bovine tuberculin. A roentgenogram of the cervical spine showed no changes in the vertebrae.

Examination of the Nervous System.—The child lay as above described, and with his eyes usually turned to the right. The upper extremities were extended, the lower flexed at the knees. Percussion of the head showed nothing unusual; there were no painful points. The right eyeslit was narrower than the left, but there was no strabismus or nystagmus. The pupils reacted promptly to light and accommodation. The corneal reflexes were lively. Fundus examination revealed a slight blurring of the edges of the disks and a mild venous hyperemia — low grade optic neuritis. The right half of the face drooped more. Hearing was normal. The tongue was extended in the median line. The palatal and pharyngeal reflexes were present.

No voluntary movements were initiated. If the right arm was raised, the patient would slowly lower it; no motion seemed possible in the opposite limb. If either leg was extended, he would gradually flex it. There was flaccid paralysis of both upper extremities. The right wrist was flexed, the right hand was a typical "ape hand." The left hand and fingers were permanently flexed. Spasm was present in the adductors of the thigh, at the knee, and in both ankles. Kernig and Brudzinski signs were not present. Ankle clonus was present, more marked on the right. The tissues were generally flabby throughout, but there were no atrophies, apparently, except in the right interossei, thenar and hypothenar groups. (Electrical reactions were not determined.)

The patient's responses to heat and cold and to touch were unreliable. To pin prick, without doubt, there was greatly diminished sensation from the second intercostal space and the second dorsal vertebra to the soles of the feet. Only on the dorsal surface of the fingers and on the anterior surface of the thighs, did any sensation appear to be present.

Tendon reflexes were everywhere present, livelier on the right than on the left.

Neither the abdominal nor cremasteric reflex was present, and only occasionally could the plantar be elicited. Positive Babinski and Oppenheim signs were found.

Alternate flushings on the right and on the left cheek, and profuse sweating over the face, head and upper part of the body were noted.

In all, four spinal punctures were made, the last being a dry puncture. The fluid had always the same characteristics. It was obtained under low pressure, and was yellow and clear on withdrawal. The immediate cyto count averaged 250 cells per c.mm., 15 per cent. polymorphonuclears, and 85 per cent. mononuclears. If heated, the fluid became solid at once. If left to stand, clots formed quickly and the fluid solidified in a short time. No tubercle bacilli or other organisms were found.

Nov. 20, 1914, the temperature suddenly rose to 41.6 C., pulse 152, and respirations 40 to 50. A maculo-papular eruption appeared on the dorsal surface of the hands and forearms. Toward night the child became semiconscious, the right pupil was larger than the left, but both still reacted to light. Strabismus and rolling of the eyes occurred intermittently. There was twitching of the body, and especially of the right face. Cheyne-Stokes breathing was observed. Nov. 21, 1914, death occurred.

CLINICAL DIAGNOSIS

The conditions presented in the foregoing case are readily separable into (1) general signs, and (2) signs specially referable to the nervous system.

1. *General Signs.*—The irregular fever, the enlarged cervical lymph nodes, the positive von Pirquet, together with the history of an illness in a previously healthy child in the second year of life, which appeared four months after measles — these signs all point, in the absence of a positive Wassermann reaction and other evidences of congenital syphilis, to a *tuberculous infection.*

2. *Signs Referable to the Nervous System.*—These may be divided into (*a*) those of spinal origin, and (*b*) those of cerebral origin.

(*a*). Spinal Signs: A pain, or paresthesia, in the right shoulder preceded a unilateral paralysis, which began in the right upper extremity, and passed to the right lower extremity. Then followed a weakness of the left shoulder girdle, and finally a complete paraplegia. Spasticity was demonstrable in the lower extremities. Sensibility to pain seemed almost completely absent below the second intercostal space (C_5). Tenderness was sharply localized over the lower cervical vertebrae. "Coagulation massive et xanthochromie" of the spinal fluid appeared as a constant phenomenon.

The Brown-Séquard syndrome, the secondary paraplegia, the segmentary distribution of the disturbances in sensation, and the localized vertebral tenderness, denote a *compression of the spinal cord, due to a circumscribed lesion.* (Schultze,[2] Oppenheim,[8] Bruns.[9]) The heavy albuminous deposit and the yellow color in the spinal fluid are also significant of pressure (Nonne[3]).

Disease external to the vertebrae, in the vertebrae themselves, or within the vertebral canal, causes compression of the spinal cord. No tumor growths of extraspinal origin were observed which by proximity or metastasis could infiltrate the bony structures. Caries and osteomas and other tumors of the vertebrae are eliminated by the short duration of the illness, the absence of severe pain, of kyphos and scoliosis, and the negative findings in the roentgenogram.

A condition within the spinal canal must then have produced the compression, and to fit the clinical picture here presented, must have involved the cord or the meninges, or both. To be considered, therefore, are meningomyelitis, pachymeningitis cervicalis hypertrophica, and tumor. An acute meningomyelitis, due to a specific organism, manifests itself as a primary disorder with an acute onset, or as a complication of an already existing process; it presents bilateral symptoms early, and, especially in children, runs a much shorter course. A myelitis luetica, limited to the spinal cord and its meninges, does not occur in very early life, and here there were no congenital stigmata and the Wassermann was negative. Tuberculous myelitis is a desseminated lesion. Pachymeningitis cervalis hypertrophica is bilateral from the start and is marked by its extreme chronicity. By the exclusion of meningomyelitis and pachymeningitis the diagnosis of *spinal tumor* is warranted.

Was the tumor intramedullary or extramedullary? The absence of definite root pains and the rapid extension of the cord symptoms suggest an intramedullary lesion; but the long-continued radicular palsy in the right upper extremity, the early right unilateral signs, the localized tenderness in the cervical vertebrae, and the tendency of the process to spread transversely and not upward (Schultze[2]), may as readily be attributed to an extramedullary lesion.

Location of the tumor: The *main-en-griffe* denotes at once the seventh and eighth cervical and first dorsal segments, with the corresponding roots of the brachial plexus. The upper limit of the segmentary distribution of the sensory disturbances (C_5) confirms this. Further evidence for this situation is the involvement of the cervical sympathetic — narrow right eyeslit, alternate flushings of both cheeks, and profuse sweating in the upper half of the body.

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[8] Oppenheim: Lehrbuch der Nervenkrankheiten, Ed. 5, Berlin, S. Karger, 1908.

[9] Bruns: Geschwülste des Nervensystems, Ed. 2, Berlin, 1908.

(*b*). Cerebral Signs: The paresis of the right side of the face, the optic neuritis of low grade, the late strabismus, the twitching and irritation of the right pupil, and the high lymphocyte count in the spinal fluid indicate meningeal irritation. A tuberculous infection was undoubtedly present elsewhere in the body, and may have been metastatic here in the brain and spinal cord as an early meningitis. The long period of unclouded consciousness, the absence of convulsions, headache and vomiting make this meningitis a matter of minor importance.

Clinical Diagnosis. Intramedullary or Extramedullary Tumor of the Spinal Cord. Compression Myelitis. Meningitis, Probably of Tuberculous Origin.

Abstract of Necropsy Report.—(Dr. E. H. Falconer).

Right Lung: In the middle lobe, and occupying about one-half of the lobe, is a hard, noncrepitant area, 4 by 2 cm. On section this tissue is necrotic and a purulent material exudes from its center. A definite capsule separates it from the surrounding tissue.

Left Lung: Scattered throughout the lung tissue are small, round areas 0.5 to 2.0 mm. in diameter, some caseous, others calcareous.

Peribronchial Lymph Nodes: These are much enlarged and hard, but show no sign of breaking down.

Intestines: The ileum shows several round, irregular, ulcerated areas 6 by 7 mm. in diameter. They seem to correspond in distribution to Peyer's patches. In the wall of the ulcer are many small, nodular, caseous areas.

Mesenteric Lymph Nodes: These are markedly enlarged and everywhere matted together. On section they show caseous areas, but with no evidence of breaking down.

Brain: There are slight congestion over the cortex and marked edema at the base, and a few scattered tubercles with considerable exudate in the meninges of pons and the circle of Willis. Immediately superior to the posterior portion of the corpus callosum, in the cingulum, and situated for the most part in the gray matter of the convolution, is a small, round, grayish-yellow mass of tissue, about 1.5 by 2.0 cm.

Microscopic Examination.—Sections of the cerebral tissue between gyri show a pia distended by exudate. This exudate consists principally of lymphoid cells and is well marked about the vessels. Large, irregular masses of caseous necrosis are scattered in the exudate. These are localized but not typical tubercles.

The Tumor: There is a zone of inflammatory reaction about the mass, as evidenced by epithelioid cells, a few lymphocytes, and congestion of the vessels. At the periphery of the tumor mass, there is an artery whose lumen is nearly closed by an obliterating endarteritis. The tumor itself consists of a pale-staining, necrotic tissue with occasional giant cells.

Cord: In the cervical enlargement, at the level of the third, fourth and fifth cervical vertebrae, considerable bulging shows beneath the dura mater, which is much congested in this area. On slitting the dura, the white substance is so soft that it exudes through the cut surface. At this level is seen an olive-shaped tumor mass, 2.5 by 1.2 cm., occupying the greater portion of the canal and flattening the cord posteriorly. It is extramedullary and does not infiltrate the cord substance proper. It has not infiltrated or become attached to the nerve roots. On section it is grayish-white, homogeneous, and of caseous appearance; there is no evidence of liquefaction.

Microscopic section of the tumor shows it to consist of a central caseous material, surrounded by epithelioid and giant cells and some lymphocytes. Beyond this there is a zone of fibrous tissue. The spinal meninges are heavily strewn with typical lymphoid tubercles, especially in the cervical and dorsal regions.

Pathologic Diagnosis.—General miliary tuberculosis. Caseous and miliary tuberculosis of lungs. Tuberculosis of bronchial and peribronchial lymph nodes. Miliary tuberculosis of spleen, liver and kidney. Tuberculous ulcers of the intestines (ileum). Miliary tuberculosis of the appendix. Tuberculosis of the mesenteric lymph nodes. Tuberculosis of the meninges of the brain and spinal cord. *Tuberculoma of the cerebrum* (cingulum), *tuberculoma of the spinal cord.*

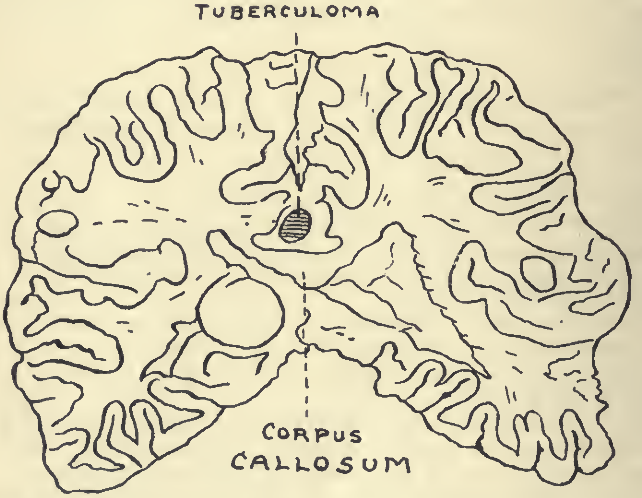

Fig. 1.—Tuberculoma of cerebral cortex (author's case).

DISCUSSION

Several rather uncommon features of this case need special consideration.

The Absence of Pain.—Pain, as a symptom, was formerly considered necessary for the establishment of a diagnosis of spinal tumor. Within the last few years, however, numerous cases have been reported in which no pain has been present. (Nonne,[10] Flatau,[4] Panski,[11] Newmark,[12] Collins and Marks,[13] and others.) "We must realize that pain and other classical data are valuable but not essential phenomena, but that the essential elements (first emphasized by Schultze) is the determination of a gradually progressive motor and sensory paralysis, the upper pole of which, despite increase of cross section and intensity, varies slightly if at all." (Collins and Marks.[13])

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[10] Nonne: Neurol. Centralbl., 1908, **27**, 749.
[11] Panski: Neurol. Centralbl., 1912, **31**, 1208.
[12] Newmark: Berl. klin. Wchnschr., 1914, No. 43, p. 739.
[13] Collins and Marks: Am. Jour. Med. Sc., June, 1915, p. 613.

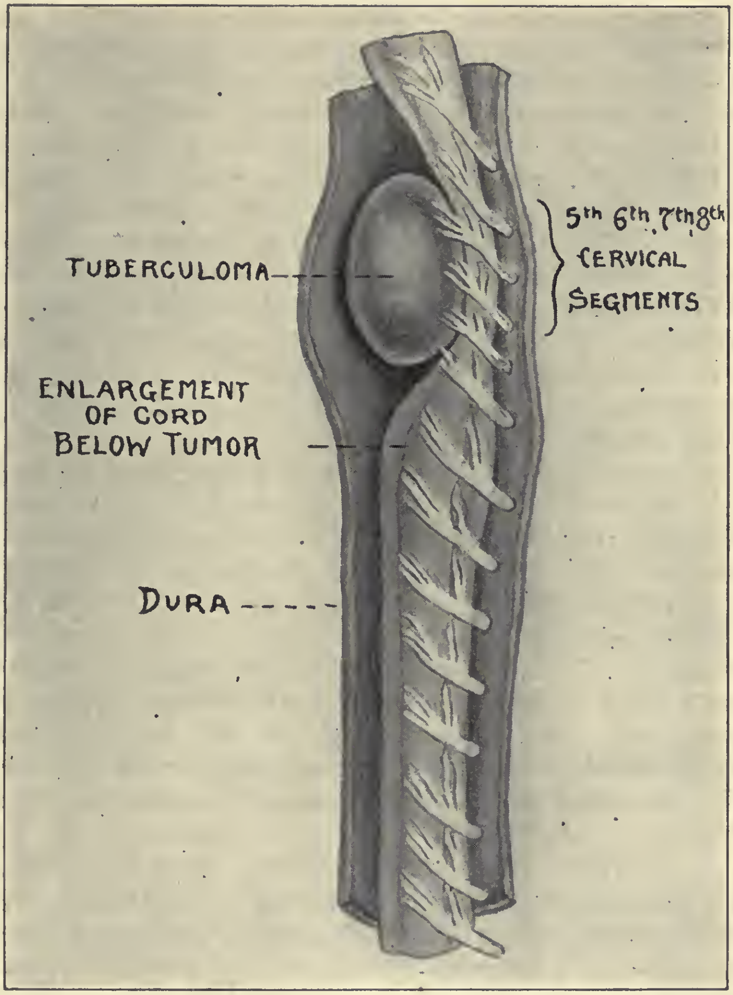
TUBERCULOMA
ENLARGEMENT OF CORD BELOW TUMOR
DURA
5th 6th 7th 8th CERVICAL SEGMENTS

Fig. 2.—Extramedullary tuberculoma of spinal cord (author's case).

Xanthochromia of the Cerebrospinal Fluid with Massive Coagulation.—Of late much attention has been paid to this appearance, first described by Froin[14] in 1903. (Mestrezat,[15] Nonne,[3] Mix,[16] Bromer,[17]

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[14] Froin: Gaz. d. hôp., 1903, **76,** 1005.

[15] Mestrezat: Le liquide cephalo-rachidien, normal et pathologique, Paris, 1912.

[16] Mix: Clinics of John B. Murphy, April, 1915.

[17] Bromer: Am. Jour. Med. Sc., March, 1916, p. 378.

Ayer and Viets.[18]) Spinal fluid of a yellow color may be divided into those with great amounts of globulin which coagulate spontaneously, and those which do not coagulate, according to Sprunt and Walker,[19] who recently studied 100 cases of xanthochromia. Fluids of the former type present what is known as Froin's Syndrome, and also as Nonne's Compression Syndrome. It always denotes a compression of the spinal cord above the site of puncture, with a consequent stasis of the fluid below the compression. The fourth lumbar puncture in this case was "dry" — there was no more fluid to evacuate. An increased lymphocytosis as an accompanying condition signifies an inflammation of the meninges. Here it was diagnostic of a tuberculous meningitis.

Position and Nature of Spinal Cord Tumors in Childhood.—Schlesinger[5] finds that meningeal tumors are more frequent in adults than in children, in whom the extramedullary tumors are usually extradural lipomas or masses of tubercle. Up to the fifth year, tumors within the cord are generally tuberculomas; later, sarcomas predominate. The tumor here under consideration was unusual both in position and pathology.

The Cerebral Growth.—This occupied a silent area, the cingulum of the cortex. No symptoms were here noted that could be traced to a brain tumor. Ziehen[20] is authority for the statement that more than 50 per cent. of all brain tumors in children are solitary tubercles, that they are multiple, that they rarely invade the cortex, but when they do, usually elect the paracentral lobule.

Prognosis.—The prognosis in spinal cord tumors of tuberculous origin is grave. Cases of temporary cure by operative procedure have been reported. (Starr,[21] Bonniger and Adler,[22] Veraguth and Brun.[23]) Until our knowledge of tuberculosis, especially tuberculosis of the central nervous system, becomes more complete, this condition will remain hopeless.

CONCLUSION

Of special clinical interest in this case report is the fact that a tumor of the spinal meninges, which was diagnosed during life, was the first manifestation of a generalized tuberculosis in a child of 19 months. Xanthochromia with massive spontaneous coagulation and pleocytosis was an attending syndrome.

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[18] Ayer and Viets: Jour. Am. Med. Assn., Dec. 6, 1916, p. 1707.

[19] Sprunt and Walker: Bull. Johns Hopkins Hosp., February, 1917, p. 80.

[20] Ziehen: Handbuch der Nervenkrankheiten im Kindesalter, Ed. 1, Berlin, S. Karger, 1912.

[21] Starr, M. Allan: Am. Jour. Med. Sc., June, 1895, p. 613.

[22] Bönniger and Adler: Med. Klin., 1911, Nos. 18-19, p. 279.

[23] Veraguth and Brun: Cor.-Bl. f. schweiz. Aerzte, 1916, No. 14; abstr., Jour. Am. Med. Assn., Nov. 26, 1916, p. 1587.

PHYSIOLOGY OF THE NEW-BORN INFANT *

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There has been an increasing amount of investigation on the metabolism of the new-born infant during the past few years, but only recently enough evidence has accumulated to be of any practical value to the general practitioner. This communication deals only with that part of the metabolism which is known as the respiratory metabolism, and from which the energy metabolism may be calculated.

The earliest study of the respiratory metabolism of the new-born infant was in 1877 by Forster,[1] who measured the carbon dioxid output of an infant 14 days old. Since then many investigators have recorded observations made by them, using different forms of apparatus. The most important of these was published in Danish in such an inaccessible form that it was overlooked in recent writings on the subject. This work by Hasselbach was reported in 1904. The original work, which is given in full in Publication 233 of the Carnegie Institution of Washington, was translated into English under the direction of Dr. Francis G. Benedict and corrected by Hasselbach himself. A detailed report of the work on the new-born done by Benedict and the writer, and a complete discussion of the literature on the physiology of the new-born may also be found in this publication.

It is necessary, before treating the subject matter of this paper, to define some of the technical terms used later.

Basal metabolism means the energy production of an infant in complete muscular repose, and may be obtained only when the baby is asleep. In one instance we found that during crying the metabolism was three times as great as when the baby was sleeping quietly. An ideal state in which to determine the basal metabolism would be the so-called "post-absorptive state" of adults; that is, when the stomach is empty; but this is rarely possible with infants, as they usually sleep only when the stomach is full. It is obvious, therefore, that only figures of the minimum or basal metabolism can be used for comparison in any instance in which the metabolism is determined for less than the so-called twenty-four-hour observation.

The *respiratory quotient* means the volume of carbon dioxid expired, divided by the volume of oxygen used. It was found when

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* Submitted for publication April 9, 1917.

* From the Nutrition Laboratory of the Carnegie Institution of Washington.

[1] Forster: Amtlicher Bericht der 50 Versammlung deutsche Naturforscher u. Aerzte in Munchen, Munich, 1877, p. 355.

pure carbohydrate was burned up outside the body that the volume of oxygen necessary for its combustion was always the same as the volume of carbon dioxid given off as a result of the combustion. The respiratory quotien of carbohydrate $\frac{CO_2}{O_2}$ is, therefore, always 1.00. The respiratory quotient of fat is 0.713, and of protein 0.801. Tables have been made from which the amount of the different food components that are being burned up in the body may be estimated, for each respiratory quotient. For example, when a respiratory quotient is 0.90, two-thirds of the energy used up comes from carbohydrate and one-third from fat.

Colostrum plays such an important part in the first three days of life that it is necessary to give a few essential facts concerning it, based on a study of the literature. The mother's breasts at birth contain only a small quantity of colostrum, which is increased under the stimulation of sucking, until the breast milk "comes in," on about the third or fourth day after birth. The energy or heat value of colostrum is about 650 calories per liter, although it may be considerably higher at times.[2] The amount of colostrum during the first twenty-four hours after birth is between 4 and 6 c.c., and gives approximately 3¼ calories. During the second day the baby receives from 78 to 129 c.c. of colostrum, or 51 to 84 calories. On the third day the amount of colostrum varies between 199 and 238 c.c., which give 129 to 154 calories. Colostrum, therefore, gives the new-born infant only a minimal amount of energy, insufficient to supply its energy requirements. It is quite natural, therefore, that it should lose weight during the colostrum period.

Loss of weight: Nearly all infants lose weight during the first few days of life, some losing more than others. This loss of weight is of two kinds: (1) "mechanical" and (2) "physiologic." The mechanical loss represents material which may be collected and weighed, and is due principally to the passage of urine and meconium, and at times to the vomiting of allantoic fluid, swallowed by the infant before birth. There is also a loss due to the evaporation of water from the skin. The physiologic loss of weight is that due to the actual oxidation of body substance as a result of metabolism, and to the fact that an infant is virtually starved during the colostrum period. The colostrum which an infant receives does not give enough food to supply the necessary energy to keep it warm. The energy and body heat must, therefore, be supplied in no small part by the glycogen in the liver and tissues. This glycogen is quickly used up and the energy is then obtained from the body fat. (See respiratory quotients, in Table 1, of the first, second and third days of life.) The body fat now assumes a very important rôle in the economy of the new-born infant, as there is not enough sugar and glycogen in the body to supply the energy necessary to keep a baby warm for more than a few hours. This fat, which was deposited during the last month of intra-uterine life, is, therefore, the storehouse of fuel and must be present in large enough amounts to supply energy until the breast milk "comes in" to take its place. Clinical experience bears out the inference that infants without a good layer of fat at birth should receive food at the earliest possible moment. This is especially true of prematurely born infants who are almost entirely devoid of fat and should be fed at a very early hour in order to conserve their strength. After the establishment of the milk supply there is a gain in body weight, the respiratory quotient rises, and the energy used by the infant is now obtained from the mother's milk instead of from its body tissues. Table 1 gives the average respiratory quotient of 105 babies.

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[2] Langstein: Rott and Edelstein: Ztschr. f. Kinderh., 1913, **7**, 210.

TABLE 1.—Average Respiratory Quotients of Infants During the First Eight Days After Birth

	First Day	Second Day	Third Day*	Fourth Day	Fifth Day	Sixth Day	Seventh Day	Eighth Day
Body weight, Kg. ...	3.48	3.41	3.32	3.34	3.43	3.51	3.54	3.82
Respiratory quotient	0.80	0.74	0.73	0.75	0.79	0.82	0.81	0.80

* Breast milk commences to "come in."

Energy requirements: It has long been thought that the "energy requirements of infants relative to the weight, are greatest during the first months of life, but gradually diminish, until at the end of the first year they are only three-fourths as great as during the first month.[3] Although this may be relatively correct after the third month, quite the reverse is true of the first and second months of life. A new-born infant requires approximately 62 calories per kilogram of body weight per twenty-four hours, but needs more as he grows older. We found that the *basal* energy requirement of infants from 1½ to 6 days of age was 44 calories per kilogram of body weight, whereas the average of a 4 to 5 months-old infant is in the neighborhood of 55 calories. It is quite probable that this discrepancy is due to the fact that the new-born infant grows fat on the very abundant supply of breast milk received during the early months of life, but muscles begin to replace the fat as the infant grows and represent a larger proportion of the body weight of the infant than at birth. The amount of heat produced depends on the amount of muscle and other "active protoplasmic tissue" in the body, and not on the fat, the heat per unit of body weight being in inverse proportion to the amount of body fat. The fatter the baby, therefore, the fewer the calories per kilogram of body weight will it require.[4] The basal metabolism of the new-born infant is also much lower than that of older infants when it is calculated per square meter of body surface, or as total heat per twenty-four hours.

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[3] Holt and Howland: Diseases of Infancy and Childhood, New York and London, 1916.

A great deal of time was spent in studying the figures obtained from observations on the new-born to find, if possible, some law that might be applicable to them. These show that the shorter infants produced less heat per square meter of body surface than the longer infants, after the first day and a half of life. The heat production per square meter of body surface was, therefore, divided by the length of the infant, and the average of the resultant figure was 12.65 calories. This figure was, therefore, taken as a constant and the following formula devised:

TABLE 2.—Body-Surface Computed from the Body-Weight by the Lissauer Formula ($10.3\sqrt[3]{wt_2}$)

Body Weight, Kg.	Body Surface, Sq. M.	Body Weight, Kg.	Body Surface, Sq. M.	Body Weight, Kg.	Body Surface, Sq. M.	Body Weight, Kg.	Body Surface, Sq. M.
2.00	0.163	2.80	0.205	3.55	0.239	4.30	0.272
2.05	0.166	2.85	0.207	3.60	0.241	4.35	0.274
2.10	0.169	2.90	0.210	3.65	0.244	4.40	0.277
2.15	0.172	2.95	0.212	3.70	0.246	4.45	0.279
2.20	0.174	3.00	0.214	3.75	0.249	4.50	0.281
2.25	0.177	3.05	0.217	3.80	0.251	4.55	0.283
2.30	0.179	3.10	0.219	3.85	0.253	4.60	0.285
2.35	0.182	3.15	0.222	3.90	0.255	4.65	0.287
2.40	0.184	3.20	0.224	3.95	0.257	4.70	0.289
2.45	0.187	3.25	0.226	4.00	0.260	4.75	0.291
2.50	0.190	3.30	0.228	4.05	0.262	4.80	0.293
2.55	0.192	3.35	0.231	4.10	0.264	4.85	0.295
2.60	0.195	3.40	0.233	4.15	0.266	4.90	0.297
2.65	0.197	3.45	0.235	4.20	0.268	4.95	0.299
2.70	0.200	3.50	0.237	4.25	0.270	5.00	0.301
2.75	0.202						

Total calories = length × 12.65 × body surface.

The body surface may be calculated from the weight of an infant by using Lissauer's formula, given in Table 2, in which the body surface is worked out for the various weights of infants. The basal metabolism may be calculated for any new-born infant of known weight and length by the use of the formula, length × 12.65 × body surface, and has been found to come within 6 per cent. of the basal metabolism actually measured in the respiratory chamber.

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[4] Benedict and Talbot: Publication 201, 1914, Carnegie Institution of Washington, and Am. Jour. Dis. Child., 1914, **8,** 1.

The metabolism during the first twenty-four to thirty-six hours of life was, on the whole, much lower than later, even when it was obtained with the same infant on successive days. In some instances this could be attributed to the fatigue incident to hard labor, but in the majority of instances the low metabolism during this period could be traced to exposure and a consequent subnormal temperature. A series of rectal temperatures showed that heat was lost from the body shortly after the water bath, when the body temperature began to fall. A subnormal temperature did not result in the more vigorous infants, who either commenced to cry or to shiver when they were cold, and thus kept the body temperature normal and produced enough heat to offset the loss from the skin. In less vigorous infants, on the other hand, the temperature became subnormal and their metabolism was correspondingly diminished, so that coincidently there must have been a depression of all the body functions, which was detrimental to the infant. In one instance the temperature dropped to 95.4 F. (35.2 C.). The writer believes, therefore, that the chilling from a water bath is the cause of death of many new-born infants, particularly premature infants, and should be entirely discarded. The baby may be satisfactorily bathed with warm oil, without evaporation and excessive loss of heat from the body.

If the new-born infant does not receive enough food during the first three or more days of life, what should be done? It is obvious that the "mechanical" loss of weight cannot be prevented, but it is quite different with the "physiologic" loss. Of the many methods suggested to prevent this loss of weight, the writer feels that the giving of breast milk within a few hours of birth is the most satisfactory. Baily and Murlin[5] suggest a mixture of cow's milk similar in composition to colostrum, which they have used with favorable results. The writer, however, feels that cow's milk should be avoided, when possible, during the early days of life, since it is a foreign protein, which may be absorbed directly into the blood and start the reaction which will either result in sensitization or immunity. "There is no time in a baby's life in which it is so easy to disturb the digestion or at which it is so difficult to correct the disturbance, if it is once caused."[6] A much better and safer procedure is to use human milk, drawn from a healthy woman, diluted if necessary with boiled water. Human milk has the advantage of being a homologous protein, of a composition adapted to the needs of the human infant. The writer has used human milk in feeding immediately after birth, for many years, with excellent results. Schick[7] tried the experiment of forcing new-born infants to take breast milk from the spoon and found that he could prevent the usual loss of weight after birth. A third method which may be used, in case human milk cannot be obtained, is to give a sterile solution of sugar and water. Theoretically, dextrose, the sugar present in the blood, is the best one to choose. Lactose and cane sugar are commonly used and have given satisfaction in America and other countries.

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[5] Bailey and Murlin: Am. Jour. Obst., 1915, **71,** 526.

[6] Morse and Talbot: The Nutrition and Feeding of Infants, New York, 1915, p. 125.

SUMMARY

1. The respiratory quotients of new-born infants indicate that the supply of glycogen in the body is quickly used up, and that the energy is obtained in large part from the body fat until the breast milk "comes in."

2. The energy requirements of new-born infants are smaller per unit of body weight than in older infants.

3. The total calories of the basal metabolism of a new-born infant may be calculated from the following formula:

Total calories = length × 12.65 × body surface.

4. Chilling from exposure or a water bath depresses the metabolism and with it all the body functions. A new-born infant should not be bathed in water, and great care should be taken that it is not chilled. Warm oil should be used to clean the body.

5. Since a new-born infant is starved until the breast milk "comes in," weak or premature infants should be fed shortly after birth, preferably with the milk of another woman; but when this is lacking, a 5 per cent. solution of some sugar such as lactose should be given as a temporary expedient.

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[7] Schick: Ztschr. f. Kinderh., December, 1915.

THE USE OF THE LONGITUDINAL SINUS FOR DIAGNOSTIC AND THERAPEUTIC MEASURES IN INFANCY *

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Owing to the fact that the examination of the blood in infants offers considerable aid in diagnosis, and that blood has been shown to be an effective medium for the introduction of therapeutic fluids, it has been necessary to look for other means of entering the blood stream than through the jugular and scalp veins, which are not always accessible, and attempts to enter them quite frequently result in failures. This is especially true in some toxic conditions in which even the external jugular is not to be seen or palpated.

Marfan, in 1898, first employed the longitudinal sinus for the intravenous injection of salt solution. Tobler, in 1915, described in detail the anatomy and technic, and Helmholz of Chicago, in the same year, described a special apparatus, useful in transfusion into the longitudinal sinus.

From the anatomic point of view, the longitudinal sinus offers the most effective route for injection of fluids or obtaining blood. The vein is rigid, cannot be pushed aside, and on entering, one gets a definite sensation of entering a vessel. The tissues that are pierced are the skin and fibrous tissue of the fontanel, each of which are about 1/8 inch in thickness, so that the average distance into the sinus is about 4/16 to 5/16 of an inch. From a series of measurements we found that the sinus grows gradually larger from before backward, so that the anterior part of the fontanel measures 3/32 inch, posterior part 3/32 to 4/32 inch, and 1 inch along the suture posterior to the fontanel, 5/32 inch, while 2 inches along the suture posterior to the fontanel it measures 5/32 to 6/32 inch. It is, therefore, advisable to enter the fontanel at the beginning of the suture just posterior to the fontanel. When one takes into consideration the fact that punctures of the ventricles can be done without harm, the damage that might result from an occasional puncture of the brain substance is negligible.

TECHNIC

The technic employed in entering the sinus is very simple and correspondingly rapid. All that is necessary is a 20 c.c. Luer syringe, with an 18 or 20 gauge needle about 1¼ inches long. The needle is

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* From The Infants' Department and Laboratory, Hospital for Sick Children.

slightly modified in two respects: first, the bevel is made about 45 degrees, so that the point does not enter the sinus deeply. Second, a guard is placed about ¼ inch from the extreme tip of the needle to prevent the latter transfixing the sinus as it passes, sometimes abruptly, through the fibrous layer of the fontanel. In the beginning, to accomplish this, a furrow was filed about the needle at the right distance from the tip, a few turns of fine silk being used to fill the furrow. At the suggestion of Dr. Arnold of Buffalo, an improvement was made on this by using solder to make an elevated ridge around the needle. The latter method is employed at present. We keep on hand a series of three or four needles with the guard varying from ¼ to 5/16 inch from the point.

In entering the sinus the needle is always first attached to the syringe to give precision in handling. If it is expected to use more than one syringe, sterile petrolatum is applied to the tip of the syringe to facilitate the detaching of the syringe from the needle when it is correctly placed in the sinus. The infant is wrapped in a sheet and held on its back on the table by one nurse, while a second sits on a chair holding the head securely in the middle line and slightly flexed. The operator stands at the side of the infant, facing it, the bevel of the needle being held parallel to the skin, so that the opening in the needle will be patent with the sinus just as soon as it is entered. Before commencing, the infant is made to cry vigorously to flood the sinus with blood. The pressure in the sinus when the infant is crying is usually sufficient to throw a jet of blood right into the syringe, if the piston be held not too firmly. Indeed, in a vigorous infant, it is surprisingly difficult to force a solution into the sinus. To overcome this difficulty and to prevent much oozing from the puncture wound, it is our custom to have the feeding, due before the injection, omitted, and then feed the infant just as soon as the needle is shown to be in the sinus. If the blood does not enter the syringe under its own pressure, it is sucked into the syringe before an injection is made.

The slight disturbance and ease with which sinus work may be done, particularly in young infants, is shown in the following instances:

A sleeping infant, 6 days old, was taken from its cot, 60 c.c. of saline, necessitating two changes of syringes, were injected into the sinus and the infant put back to bed without awakening.

The same day a second infant was given 40 c.c. of saline solution, the infant rousing only when the needle was inserted, but at once going off to sleep for the remainder of the injection.

A third instance, showing a practical application of the method, was that in which blood for a Wassermann was obtained from a patient in one of our own offices, the mother holding the infant, and not realizing that blood had been withdrawn, as the operation was done quickly with the syringe obscured by gauze.

THE EFFECT OF TRANSFIXING THE SINUS BY THE NEEDLE. A REPORT OF FOUR CASES

In the early part of our sinus work it was thought that the infant might be endangered or some untoward symptom be caused by transfixing the sinus. In our experience the accident has happened four times, in none of which was there any clinical sign, such as cortical irritation, nor in the two cases which came to necropsy, was any anatomic sign, such as hemorrhage, visible. The first two cases occurred before a guard was used on the needle to prevent it entering too deeply. In both cases the operator was obtaining blood for a Wassermann reaction. In the second instance about 5 c.c. of cerebrospinal fluid was first drawn into the syringe, and then, withdrawing the needle along the line of entrance, 5 c.c. of blood were obtained, showing that the needle had transfixed the sinus.

Case 3 was in an infant dying of malnutrition, in which the family history suggested syphilis. The silk gauze slipped, allowing the needle to enter about ¾ inch; withdrawing along the line of entrance, blood was obtained, showing that the needle had transfixed the sinus. The infant died five hours afterward. The necropsy revealed no signs of hemorrhage, and showed no microscopic damage done to the sinus.

Case 4 was in an infant dying of miliary tuberculosis in which the whole venous circulation was markedly distended. The sinus was transfixed in two places. The necropsy, four hours afterward, showed the sinus and cerebral veins markedly distended, but an asbsence of clot or sign of injury. This case was thought to be very instructive, for, in view of the marked distention of the sinus, it was the type of case in which one would expect hemorrhage, if it ever occurred. Clinically and anatomically up to the present we have seen no bad results from transfixing the sinus.

In this paper we are able to report 100 cases in which the sinus has been used either for diagnosis or for therapeutic measures. Blood has been withdrawn for a Wassermann test in thirty-nine cases, ranging in age from birth to the oldest, 2 years and 5 months. In the latter the anterior fontanel was 1 inch across and ½ inch in the anteroposterior direction. It was quite firm, but fibrous, and presented no more difficulty in entering the sinus than one would expect from the nature of the tissue at that age. In these cases and the remaining cases the sinus was entered in one or more of three locations: first, the anterior angle of the fontanel; second, the posterior angle of the fontanel; third, along the line of the sagittal suture at a distance of ½ to 1½ inches behind the fontanel. We have been equally successful in the three locations, and think that, usually, the one has no advantage over the others. The three locations, however, give three chances for entering the sinus if any difficulty, as occasionally happens, is encountered.

THERAPEUTIC MEASURES

Diphtheritic Antitoxin.—This has been given in two instances, one being in a ward case, and the second, in an infant seen in consultation, 3 weeks old, with a bad diphtheritic throat of three days' duration, extremely ill, the infant having had no serum. It was thought that the only chance of saving the infant was by the intravenous injection of a large dose of antitoxin. Twenty-thousand units were accordingly given, by means of the sinus route, in a few minutes. This method of giving antitoxin intravenously should prove very valuable and save lives that otherwise might be lost.

Diarsenol.—It was with the view of giving the most intensive treatment for syphilitic infants that we first turned to the sinus in our search for a method of doing this easily and rapidly. Up to the present we have given fifty-two injections by this method. When one remembers the areas of necrosis following accidental subcutaneous injection of diarsenol or salvarsan, this fact will be apparent, that the injection is a good test of the efficiency of the sinus in therapeutic treatments. No cases have occurred in which irritation has followed the injection of the arsenical salts. In one instance adhesions or thrombosis may have occurred, although our only ground for suspecting this was the difficulty experienced in entering the sinus after six injections had been given. This was the first case in which we had given the diarsenol this way and our difficulty may have been due to lack of experience. The case went on to complete recovery, however, with repeated negative Wassermann tests. In all our other cases we have had no difficulty in giving repeated doses, so that we feel justified in concluding that thrombosis practically never occurs in the sinus as it does occasionally in the small veins following the injections.

Saline Injections.—Having in view the use of the sinus for transfusing purposes, four infants were given a saline solution, using the 20 c.c. syringe to see if any difficulty would arise while changing the syringes with the needle in the sinus. It was found by putting petrolatum on the top of the syringe, and with an assistant preventing the needle from turning by means of an artery forceps, that the syringes could be removed and replaced without any difficulty. Judging, from these saline cases, the ease and rapidity with which the solution was injected, there is no doubt that an infant could be given 100 c.c. or more of blood in a few minutes. The most interesting and practical point is that this could be carried out at the bedside and with only a few minutes' preparation. To emphasize the ease and rapidity of an injection, it may be added that four injections of diarsenol have been given by one of us in fifteen minutes, this including the preparation of each individual dose, the preparations of the infants, etc. Anyone who has worked with the veins in infants will appreciate the importance of this statement as an evidence of the value of this procedure as a time saver.

Blood Culture. — Three cases for blood culture by the Rosenau method were carried out. There was no difficulty in getting sufficient blood, the parts being easily prepared and rendered aseptic. We have in mind the use of the sinus for giving sodium bicarbonate solution and for other therapeutic measures, but owing to being short handed and having had extra work thrown on us, we are unable to report these cases at present.

THE PRODROMAL SYMPTOMS OF INFANTILE PARALYSIS

BASED ON A STUDY OF 400 HISTORIES OF PATIENTS ADMITTED TO THE WILLARD PARKER HOSPITAL FROM JULY 1 TO SEPTEMBER 1, 1916, INCLUSIVE *

MAY G. WILSON, M.D.
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These histories were obtained by personal interviews with parents, corroborated, when possible, by family physicians. Every effort was made to obtain an accurate history of the onset and course of the illness prior to admission. The wide publicity given this disease resulted in the early recognition and unusually close observation of the illness and symptoms of the child.

The symptoms included in this report were those noted from the onset of illness until the appearance of paralysis. Falls, overexertion, unusual excitement, overeating, and dentition preceding the onset were given as causes. The onset as a rule, was acute, attacking an apparently healthy child unawares.

I will take up the prominent prodromal symptoms in the following order: Fever, gastro-intestinal symptoms, respiratory symptoms, nervous symptoms, urinary system, skin.

Fever.—Fever was the most constant initial symptom, being noted in 334 cases. Only 2 per cent., on careful investigation, gave no history of fever, the temperature rapidly reaching its fastigium in twenty-four to forty-eight hours. The highest temperature noted was 106 degrees, the average, 103; duration, from one to ten days, average duration, four days, falling by crisis or lysis.

The following tabulation and Chart 1 show the relation of the duration of the fever to the day of the disease.

Fever	Days	Cases
0	..	8
..	1	17
..	2	45
..	3	71
..	4	63
..	5	39
..	6	27
..	7	21
..	8	6
..	9	2
..	10	4
..	11	1

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* Submitted for publication April 9, 1917.

* Read before the New York Academy of Medicine, Pediatric Section, Oct. 12, 1916.

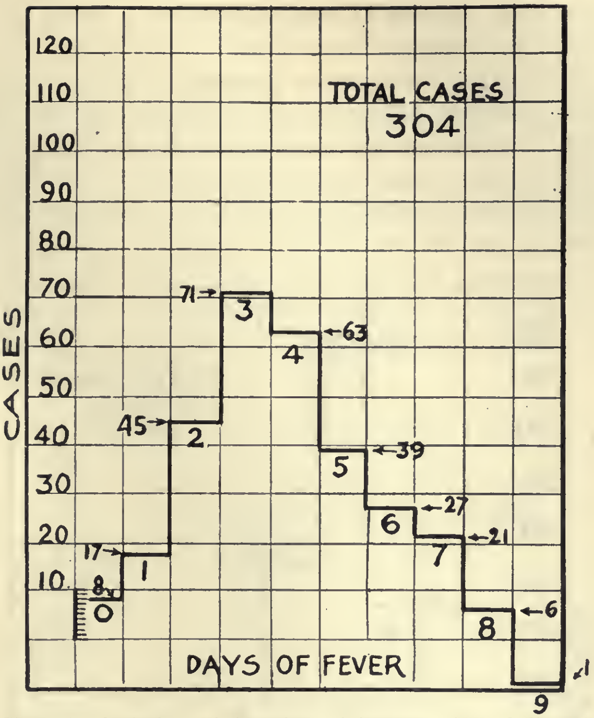

Chart 1.—Relation of duration of fever to day of disease.

In cases of remission or relapse, an initial fever of one or two days was followed by apparent health from two to six days, with a secondary fever, and ensuing paralysis.

The following tabulation and Chart 2 show the relation of the onset of paralysis to the day of the disease.

Paralysis	Days	Cases
0	..	6
..	1	10
..	2	67
..	3	120
..	4	79
..	5	27
..	6	12
..	7	10
..	8	1
..	9	1

Gastro-Intestinal Symptoms.—Vomiting: This was noted as an initial symptom in sixty-seven cases, as an early symptom in 132, sometimes occurring after the child had retired in apparently good health and slept a while; more usually, however, immediately on taking food. The vomiting was seldom repeated; in one instance it was of a projectile character.

Constipation: One hundred and fifty-six cases gave a definite history of persistent constipation for two or more days, resisting ordinary catharsis, and only relieved by repeated enemas. Fecal scybali were often found on examination.

Diarrhea: Diarrhea was not a common symptom in this series, being present in only twenty-five cases, and being neither severe nor characteristic. Abdominal pain was noted as an initial symptom in twenty-one cases, as an early symptom in twenty-five. When present, it was usually severe, persisting several days, referred to the epigastrium or general, and in two instances simulating appendicitis.

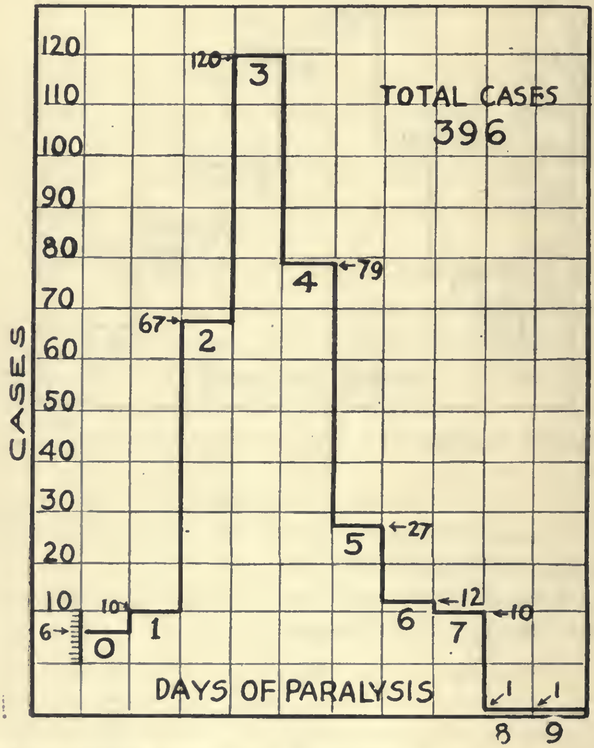

Chart 2.—The relation of the onset of paralysis to the day of the disease.

Respiratory Symptoms.—Throat: As an initial symptom, sore throat was complained of in 21 cases. A red throat was noted in 27 cases, follicular tonsillitis in 14. On examination of 100 cases on admission, injected fauces were found in 31 cases, enlarged inflamed tonsils in 11, exudate in 3, mucopurulent, frothy discharge in 7.

Epistaxis was present in two cases as an initial symptom.

Coryza was present in seventeen cases.

Conjuctivitis was present in nine cases.

Cough was present in thirty-eight cases, usually slight; two instances of severe bronchitis were noted. As a group, these symptoms were not common or characteristic.

Nervous Symptoms.—Drowsiness: Persistent drowsiness was an early and characteristic symptom, noted in 288 cases; that is, 72 per cent., varying from slight apathy to stupor in forty-seven cases. As one mother stated: "The baby just wanted to sleep all the time, and I had to keep him awake to nurse him." It was of common occurrence in the admitting room to find children sound asleep and difficult to arouse, in spite of their strange surroundings and long ride in the ambulance.

Irritability was next in frequency, noted in 153 cases. Associated with this symptom was marked hyperesthesia, noted in ninety-seven cases, the slightest touch or even approach being resented. "My baby is sore all over," said a mother.

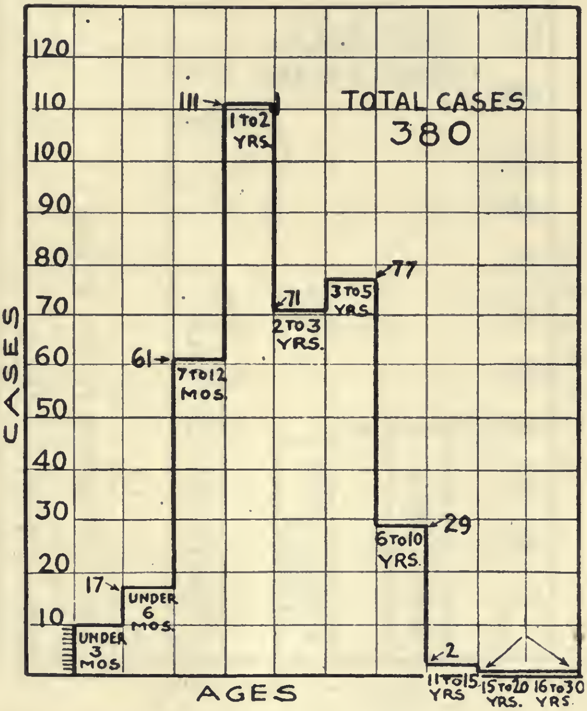

Chart 3.—Age incidence.

Tenderness and stiffness of the neck was an early and common symptom, noted in 161 cases. Retraction of the neck and flexion of the lower extremities appeared in forty cases.

Pain was present in 130 cases, usually referred to extremities, neck, back, shoulders and chest.

Tremor was noted in 113 cases, sometimes limited to a single muscle or group of muscles, usually of the extremities. Parents would remark: "Child seemed to shiver," or, "I first noticed when Mary took a piece of bread how her hands trembled like an old man's." Tremor persisted during the febrile period, preceding the paralysis by twenty-four to forty-eight hours. Two cases showed a marked, coarse tremor, persisting for several weeks, limited to one side of the body, resembling intention tremor, absent when asleep and recurring on the slightest irritation.

Twitching was noted in sixty-four cases, sometimes choreiform. Twitching of the corner of the mouth often preceded a facial paralysis.

Headache was present in seventy-eight cases, often persistent and severe; frontal or general headache was the first symptom complained of in twelve cases. Convulsions were present in six cases, as an initial symptom in three. Two cases were of children giving histories of previous convulsions.

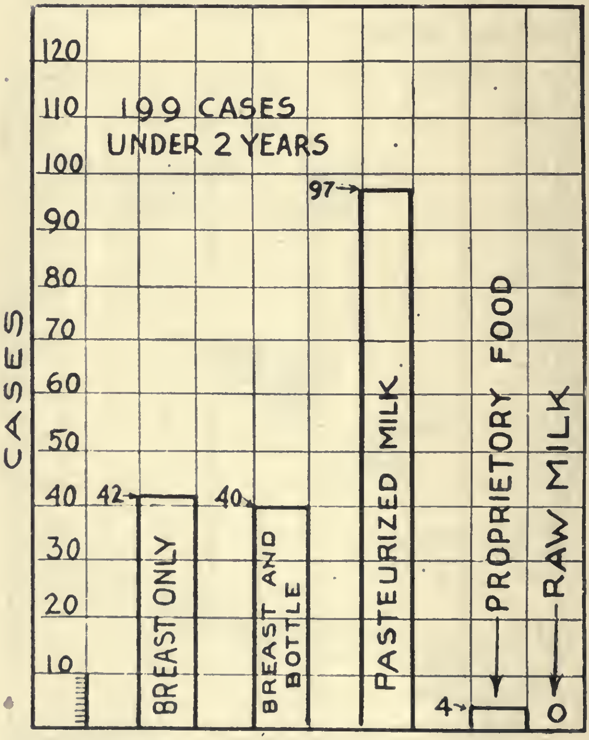

Chart 4.—Previous feeding.

Delirium was noted in ten cases.

Urinary System.—Twenty-one cases gave a history of some urinary disturbance, usually minor retention.

Skin.—There was noted profuse sweating in forty-five cases, and out of proportion to the fever present, usually preceding the paralysis, and as a rule, general; in a few instances, localized.

Rash: Red blotches on extremities, 2 cases; general erythema, 4 cases; macular, resembling measles, 8 cases; urticaria, 4 cases; pustular, 2 cases; herpes, 7 cases, over back and trunk, and in one case limited to arm later paralyzed.

The clinical picture of the abortive type of the disease corresponds in general with the initial stage of a typical case followed by paralysis. Mild initial symptoms may be followed by extensive paralysis, and, on the other hand, cases with severe and alarming onset have shown slight paralysis and rapid recovery.

In this series the ages were (Chart 3):

Under 3 months, 10.
7 to 12 months, 61.
1 to 2 years, 111.
2 to 3 years, 71.
3 to 5 years, 77.
6 to 10 years, 29.
11 to 15 years, 2.
16 to 30 years, 2.

Sex: 222 males and 178 females.

The race incidence was as follows:

Hebrew, 152
American, 76
Italian, 70
Irish, 50
Polish, 17
German, 6
Colored, 6
Swedish, 4
Japanese, 1

Previous contagious diseases:

Measles, 45
Scarlet fever, 6
Diphtheria, 4
Chickenpox, 4
Whooping cough, 7

Twelve cases had had recent operations on the tonsils, 8 had hypertrophied tonsils and 87 had normal tonsils.

Of 537 exposures in the families in which the disease occurred there were 50 secondary cases.

Of the previous feeding it was ascertained as follows (Chart 4):

	Cases
Breast only	42
Breast and bottle (pasteurized milk) (Grades A and B)	40
Breast and bottle (condensed milk)	3
Bottle only (pasteurized milk) (Grades A and B)	97
Bottle only (condensed milk)	2
Bottle only (malted milk)	2
Bottle only (Nèstle's food)	1

As to summer errors of diet, that is, ice cream, soda water, candy, pastries, watermelon, spoiled fruits, 163 out of a total of 292 children over 2 years old gave a history of over indulgence in this respect.

REPORT OF CASES

The following case histories illustrate the various symptoms of onset:

Case 1.—Girl, aged 27 months; onset, Saturday, August 12, with high fever. Vomited breakfast; increasing drowsiness; bowels constipated; twitching of the corner of the mouth. Sunday, a. m., twenty-four hours after onset, facial paralysis was noted. Monday, p. m., temperature normal; child well except for facial paralysis. Discharged October 14 with slight facial paralysis.

Case 2.—Girl, aged 7½ years; onset, Thursday, July 27, with severe frontal headache. Vomited breakfast; temperature 105. The child was extremely irritable, complained of pain in the extremities, stiffness of the neck and general twitching. Sunday, July 30, the fourth day of the disease, paralysis of legs and arms was observed. Discharged October 1, with paralysis of legs and arms.

Case 3.—Girl, aged 2½, sister of the patient, Case 2. Gave the following history: For the previous week the child complained of general malaise, headache and abdominal pain. July 31, the child was up and about. August 1, took to bed with high fever, headache and abdominal pain. Vomited. August 3 and 4, became increasingly drowsy, going into coma, August 5. Admitted August 6, with temperature 103. August 17, normal temperature. Child fully recovered; no paralysis. Discharged October 1.

Case 4.—Boy, aged 3, one of twins. Onset Wednesday, August 10. Wednesday, August 10, the child was playing as usual, but spent a restless night with high fever. Thursday the child was unusually sleepy and remained in bed. The bowels were constipated; complained of headache, but did not seem ill. On Saturday morning, except for the bowels not moving, the child seemed much better. Saturday, p. m., there was a marked change; twitching of the hands, a sudden difficulty in breathing and rattling in the chest. The child was admitted to the hospital at 6 p. m. and died in three hours of respiratory paralysis.

Case 5.—Boy, one of twins, aged 20 months. (Brother died after three days' illness, July 9.) July 10, the patient had high fever, tonsillitis, constipation; child became increasingly drowsy; was irritable and did not want to be taken up. July 12, admitted to hospital; sore throat, fever, drowsy. July 14, two days later, the child was well, but very weak. July 15, third day, the child was apparently normal and was almost considered as a "no case" by one of the attending physicians who had not seen the child before.

Case 6.—Boy, aged 20 months (brother, 3 years of age, died after an illness, July 10 to July 13, of respiratory paralysis). Onset, July 17; first symptoms vomiting, fever, increasing drowsiness, profuse sweating. July 19, mother noticed the child could not lift the upper lids of both eyes. Admitted July 20; temperature 100.5, pulse 110, respiration 30; stuporous; erythematous rash over body. The only paralysis noted was that of both upper lids. July 26, the child was standing in his crib, apparently well, but not being able to lift both eyelids.

Case 7.—Woman, married, aged 28. Onset July 31; severe frontal headache, fever; vomited; had backache and abdominal pain and some cough. She thought she had caught cold. She took to bed August 1; sweat profusely, the symptoms of onset persisting. August 2, felt weakness in the right leg; by the next day it affected her left leg and she was unable to move it. August 3, sharp pains in both lower extremities; especially painful to the touch in the course of the nerves. On admission, August 4, there was paralysis of both lower extremities.

Case 8.—Boy, aged 3½ years. Onset August 8. First symptom, headache; vomited. Was better the next day and was up and about. August 10, he became apathetic; had projectile vomiting all day; complained of pain in the head. Became increasingly drowsy; could not stand or sit up; was very sensitive to touch; had some stiffness of the neck and back. Admitted August 11; temperature 101; stuporous; eyes did not coordinate; muscular weakness of right and left deltoid and right and left quadriceps extensors. All reflexes absent. The child was seen January 1; no residual paralysis.

Case 9.—Girl, colored, aged 4 years. Onset August 6, with fever, difficulty in breathing, increasing drowsiness, obstinate constipation. On the second day, twitching of extremities; cried out with pain in the head; was very sensitive to touch and had some cough. On the third day, weakness of the right and left deltoid. Admission August 9; temperature 102, pulse 140, respiration 38; throat slightly congested; sensorium cloudy; paralysis of upper extremity and intercostals, with weakness of lower extremity; all reflexes exaggerated. The child died August 17 of respiratory paralysis.

Case 10.—Boy, aged 7 years. Onset August 3; first symptoms, fever, vomiting, abdominal pain. Persistent headache; increasing drowsiness. August 6, patient became delirious and got out of bed. Admitted August 8. Throat congested; chest clear; abdomen tender and distended; sensorium cloudy; no definite paralysis noted; all reflexes exaggerated; spinal sign present. August 9, patient semistuporous; scaphoid abdomen; retention of urine. August 11, weakness of both deltoids; reflexes absent. August 12, general condition very much improved. August 13, paralysis of both deltoids. August 17, general condition normal; paralysis of both deltoids present.

Case 11.—Girl, aged 7 years. Onset July 26, with fever; vomited several times; was extremely irritable and did not wish to be handled; complained of headache and pain in the throat. July 27, sweat profusely; was drowsy and voice became hoarse; had difficulty in swallowing. Admitted to the hospital, July 28; temperature 101; paralysis of the muscles of deglutition and laryngeal involvement. Died July 30.

CONCLUSION

The prodromal period has been found to be the most important stage in the course of the disease, both as to early quarantine and treatment. A careful history, while not diagnostic, is very suggestive, particularly in an epidemic.

I wish to express my thanks to the director, visiting and resident staff of the Willard Parker Hospital for the opportunity and cooperation afforded me in this study.

601 West 177th St.

POSTERIOR BASIC (WALLED-OFF) MENINGITIS. REPORT OF A CASE WITH RECOVERY *

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Recovery after the development of "walled-off" meningitis is rare. Fisher[1] reported the first case recovery in a child. Verbizer and Chauvel[2] report recovery in an adult.

REPORT OF CASE

History.—A child, 11 months old, a patient of Dr. Saulberry, developed meningococcic meningitis. Serum treatment was begun late, two weeks after the onset, and was discontinued in the presence of a severe, persistent hydrocephalus, owing to objection by the parents. Four weeks after the onset the child presented the classical picture of "basic" meningitis; opisthotonos was marked, the eyes were wide open, staring, with lids retracted, the face expressionless. Hydrocephalus was extreme; head large, fontanel bulging, sutures widely separated. The heart's action was very irregular; respirations were irregular, of the Biot type. There was persistent tonic spasm of the extremities, with occasional clonic convulsions. Vomiting was repeated and projectile. The temperature reached 102 F., and was of irregular type.

Diagnosis.—Lumbar puncture at two levels yielded a few drops of clear, sterile cerebrospinal fluid. The clinical picture of hydrocephalus, meningeal irritation and absence of fluid in the subarachnoid space pointed to an encapsulated (walled-off) hydrocephalus, due to a closure of the foramina of Key, Retzius and Majendie.

Management.—Ventricular puncture was indicated. An ordinary lumbar puncture needle, with stylet attached, was introduced into the right ventricle through the extreme lateral border of the anterior fontanel. The needle was directed downward, backward and inward, and the ventricle was reached at a depth of about 2 inches. Fifty cubic centimeters of slightly turbid fluid under very high pressure were removed and 20 c.c. of serum injected. There was a fall of 10 mm. Hg in blood pressure on the removal of the fluid, but no change on injecting the serum. The left ventricle was tapped the next day, 80 c.c. of turbid fluid removed and 20 c.c. of serum injected, with blood pressure change as on the previous day. The first fluid showed many pus cells and a few meningococci, extracellular and intracellular; the second specimen had only a few pus cells and intracellular organisms.

The right ventricle was tapped forty-eight hours later and 60 c.c. of clear fluid were removed. No meningococci were found. There was marked clinical improvement. The parents at this stage decided against any further intracerebral treatment. Improvement continued, however, and two weeks later the child had apparently recovered completely, with no obvious sequelae.

Subsequent Course.—Two months later the child presented a most unusual picture. He was bright, and had grown tremendously, having put on in two months the equivalent growth of a year and a half. He was active, playful,

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* Submitted for publication April 14, 1917.

[1] Fisher: New York Med. Jour., March 26, 1910.

[2] Verbizer and Chauvel: Bull. et mém. Soc. méd. d. hôp. de Paris, 1916, **32.**

could see well, and had developed mentally almost in proportion to his skeletal growth. There was a large thymus. The head was large. During the previous month, however, the child had developed alarming spells of unconsciousness, marked cyanosis and dyspnea, lasting a few minutes; at first occurring every few days, then several times daily. I interpreted the condition as being due to a persistent hydrocephalus, and attributed the excessive skeletal development to pituitary involvement.

Lumbar puncture yielded 60 c.c. of clear sterile fluid under high pressure. The puncture proved that the communication between the ventricles and subarachnoid space had been reestablished. There were no convulsions for three days, and during the following two weeks convulsions occurred at infrequent intervals. Thyroid extract was administered.

A year later I learned that the child had grown very stout and large for his age, but was somewhat subnormal mentally. The attacks of cyanosis ceased a few months after the last puncture.

This case proved not only that recovery is possible, but that the communication between ventricles and subarachnoid space can be reestablished.

Various methods may be used to drain the ventricles. The simplest is puncture through the anterior fontanel, with or without drainage by tube or silk passing from without into the ventricles.[3] When the fontanel is closed, Kocher's point for trephining over the anterior fontanel, or Keene's point for the posterior horn of the ventricle, may be selected. Haynes'[4] cisternasinus drainage is intended to direct the cerebrospinal fluid into one of the brain sinuses. Sharp[5] describes the treatment of internal hydrocephalus by introducing linen strands into the ventricle and bringing the ends out through the temporal muscle and fascia, obtaining drainage in this way. Haynes' and Sharpe's methods are only applicable in that type of basic meningitis with sterile ventricular cerebrospinal fluid.

The most important requisites for successful results are early diagnosis and immediate intraventricular treatment. More important, however, is the prevention of this complication of simple epidemic meningitis. The secret is early diagnosis, early and persistent intraspinal serum treatment, and control of hydrocephalus.

Holmes and Twenty-Third Street.

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[3] Sophian, A.: Epidemic Meningitis, St. Louis, 1913.

[4] Haynes: New York State Jour. Med., 1916, **16**, 174.

[5] Sharp: Am. Jour. Med. Sc., April, 1917.

PROGRESS IN PEDIATRICS

REVIEW OF OPHTHALMOLOGY *

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Amaurotic Family Idiocy.—Amaurotic family idiocy is a disease of the central (cerebral) nervous system in which the principal symptoms consist in gradually increasing physical weakness, arrested mental development and gradual loss of sight. It is found almost exclusively in Jewish children 2 or 3 years of age, although a few cases have been reported in children of other nationalities.

Ophthalmoscopic examination shows a whitening optic nerve and a deep red round spot in the fovea, surrounded by a whitish patch of retinal degeneration. The disease is fatal in the course of a few months.

The clinical similarity of amaurotic family idiocy to "cerebral family degeneration" has led to the belief that they are identical affections, and that the latter title is given to the affection in its later stages. Batten and Mayou[1] say:

> There is a close relationship between these cases (family cerebral degeneration) and the cases of amaurotic idiocy. The only difference in the two diseases appears to be that the macular region in amaurotic family idiocy shows a much more marked edema of the internuclear layers, and therefore. a white area around the macula which is associated with a hole or thinning of the retina at the fovea, due to edema.

The late George Coats[2] dissents from this description of the histology of the retina in amaurotic family idiocy. He says that the changes are absolutely confined to the ganglion cell and nerve fiber layers; that there is no edema, folding, thinning, or formation of holes at the fovea. The pathology of family cerebral degeneration is: (1) Certain cytologic degenerations of the ganglion cells; (2) a diminution amounting in places to a complete disappearance of those elements; (3) edema of the internuclear layer; (4) loss of rods and cones and of the outer nuclear layers; (5) thickening of the supporting elements; (6) immigration of pigment into the outer layers of the retina.

Another point brought out by Mr. Coats, observed and commented on by other observers, is that sudden local obstruction of the circula-

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* Submitted for publication Feb. 25, 1917.

[1] Batten and Mayou: Proc. Roy. Soc. Med., 1915, **8**, Ophth. Sect.

[2] Coats: Ophthalmoscope, April, 1916.

tion, as in thrombus of the central artery of the retina, does not produce edema of the neighboring tissues, or the tissues previously supplied by the artery, as has been until recently held, but an acute coagulation necrosis. In support of this view, he says:

> 1. Nowhere in the body does obstruction of an artery cause edema. The changes are a white infarct of the inner layers, which receive their supply from the central artery. 2. The ophthalmoscopic appearances produced by macular edema are well known and may be studied in cases of nephritis and papilledema. They differ in that the opacity is never nearly so dense and there is no cherry spot. 3. The distribution of the opacity is at variance with the hypothesis that it results from edema. If due to that cause the opacity should be present in the periphery as well as in the macula. 4. Edema offers no explanation of the fact that the opacity always persists for about the same time—the period required for the breaking down and absorption of the necrotic layers, not for the absorption of the edema, for it is certain that the rapidity and completeness of the restoration of the circulation is subject to very large variations.

Congenital Glaucoma and Some Allied Conditions.—This disease is better known as buphthalmos or hydrophthalmus.[3] It is, although not always recognized in infancy, congenital in origin, and dependent on defective development of the parts concerned in excretion; bilateral in 63 per cent. of the cases, and twice as common among boys as among girls. The symptoms are slow but steady enlargement of the eye; hemispherical or globular cornea; greatly deepened anterior chamber; uniformly distended sclera; tremulous iris; increase of intra-ocular pressure; cupping of the optic disk; marked impairment of vision. The affection is an arrest of development and is due to obstruction of excretion (rather than the result of inflammation) through closure or absence of the filtration angle in the anterior chamber. He advises trephining as the most satisfactory surgical cure, and adds that we must never forget the possibility that congenital syphilis may be playing a part in any case of buphthalmos, and that we must consequently order our methods of diagnosis and our therapy in the light of this knowledge.

Interstitial Keratitis.—Dr. George F. Suker,[4] in a discussion of the use of salvarsan and neosalvarsan in the treatment of interstitial keratitis, says that it makes no difference whether antispecific treatment is employed or not, as the patient will improve under general treatment. He modifies this statement, however, by admitting that salvarsan is of value when the spirochetes are present in the corneal tissue proper. When a local reaction, as shown by circumcorneal injection, follows the initial dose of salvarsan the spirochetes are frequently found in the corneal stroma. Therefore, salvarsan acts somewhat after the manner of tuberculin, and in such cases a marked improvement follows its use.

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[3] Elliot, R. H.: Ophth. Rec., November, 1916.

[4] Suker, G. F.: Ophth. Rec., November, 1916.

Myopia.—Increase in length of the anteroposterior axis of the eyeball is rarely congenital and seldom found in children under 10 years of age. But that myopia does exist at an early age is shown by reports by Harman,[5] Snell[6] and Walker.[7] Tenner[8] notes that myopia, whether present or not at the beginning of school life, may develop and gradually increase with age so that at 16 years refraction of the ball has increased in nearly one-half of the children who have inherited a tendency to myopia.

The correction of hyperopia and astigmatism would prevent the stretching of the sclera, and hence myopia, in many instances. In addition to the careful correction of refraction under paralysis of accommodation, Crampton[9] says the attention of the guardian or teacher should be directed to other aids, such as the correction of faulty habits, including excessive use of the eyes for near work; tendency to stooping, and the proper adaptation of desks to the size of the student and the source of illumination.

Trachoma.—The surgical treatment of trachoma, the scourge of every country and every people, has been the subject of many recent papers, and each writer seems to believe that the method employed by him is the only one and that will effect a cure in most cases. Despite the laboratory investigations, no progress has been made in the discovery of the cause, and until the etiology is better understood the value of any treatment must remain problematic.

The primary objects of treatment are, according to Wright,[10] to minimize conjunctival hypertrophy; to produce prompt absorption or removal of existing granulations; to prevent extensive destruction of the conjunctival mucosa; to limit secretion and guard against complications which seriously endanger corneal integrity; to restore the damaged structures, and to prevent deformity and impairment of vision.

The surgery embraces expression by manual manipulation or by forceps; vigorous rubbing of the conjunctiva with 1 to 5,000 mercuric chlorid solution; the subcutaneous injection of the contents of the trachoma follicles triturated in a saline solution; grattage; rolling and rubbing the bleeding surface with gauze saturated with a solution of mercuric cyanid; expression, followed by resection of the tarsal conjunctiva; electrolysis; removal of the tarsal cartilage and palpebral conjunctiva; radium; the Finsen ray.

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[5] Harman: Proc. Roy. Soc. Med., Nov. 4, 1914, Ophth. Sect.

[6] Snell: Ophth. Rev., 1915, **34**, 95.

[7] Walker: Ophth. Rev., 1915, **34**, 191.

[8] Tenner: New York Med. Jour., 1915, **102**, 611.

[9] Crampton: Am. Jour. Ophth., 1915, **32**, 86.

[10] Wright: Internat. Clin., Series 25, 1915, **3**, 62.

The latest medicinal or bacteriologic remedy consists in the use of tablets containing the Bulgarian bacillus. C. R. Hudgel[11] reports the following case:

> A patient with trachoma in the second stage came under my care. I reduced the tablets to a fine powder, everted and scarified the lids and dusted the powder on the lids night and morning. The pannus disappeared and in two weeks the patient was well.

Daggett (*Amer. Jour. Clin. Med.*, July, 1913) also has had success with the Bulgarian bacillus.

Crawford of Nashville used this remedy in fourteen cases and claims surprisingly good results.

Eye Signs of Poliomyelitis.—During the epidemic of poliomyelitis of 1916, no writer has, as far as it is possible to learn, laid much stress on eye signs or symptoms, or pointed out that the involvement of the eyes might indicate the presence of this affection rather than other forms of disease of the cerebrospinal system. The value of eye signs in determining the diagnosis may accordingly be regarded as negative.

An isolated extra-ocular paralysis or even a monocular or binocular optic neuritis are not significant of any definite lesion, and are found in many diseases of the cerebrospinal system. As C. H. Fife[12] says: "An infectious disease that may involve practically any portion of the cerebrospinal axis necessarily presents a varied and kaleidoscopic symptomatology." In the lengthy and able discussion following the reading of his paper the only mention of ocular involvement was made by T. H. Weisenburg, who had studied about six hundred cases of poliomyelitis admitted to the Municipal Hospital of Philadelphia. He said:

> There have been a large number of bulbar cases; in these the seventh nerve is generally implicated, although in my own examinations I found, as a rule, an associated paralysis of the sixth and fifth nerves. Paralysis of the ocular group is very uncommon. Blindness I have seen only once.

Posey[13] reports one case of primary double optic nerve atrophy, one of paralysis of the sixth and seventh nerves, one of double ptosis (he expressed himself as uncertain as to whether the ptosis had not antedated the attack of poliomyelitis), and one of complete external ophthalmoplegia. As to the origin of the ocular paralysis, Weisenburg says:

> I am in doubt as to the meningeal origin of the optic nerve atrophy or muscular palsies in infantile paralysis. I have failed to detect what I would consider either an anterior or posterior root lesion, or a cranial nerve lesion due to meningitis, for while the pathology of the disease is undoubtedly a meningomyelitis, yet the meningeal lesions are not sufficient to cause pathologic manifestations for any length of time.

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11. Hudgel: Northwest Med., June, 1914.
12. Fife: Pennsylvania Med. Jour., November, 1916.
13. Posey: Ophth. Rec., December, 1916.

Ethylhydrocuprein.—Among the newer remedies which has proved its worth in a large number of clinical trials is ethylhydrocuprein, a derivative of quinin. Its name is misleading, for unless one knows its family connections one is apt to believe it to be a form of copper. This error is not infrequent. It is also known as "optochin." Its special prerogative is inflammation due to the presence of the pneumococcus, although it has been recommended when the affection is due to the staphylococcus, the streptococcus, the gonococcus, and to mixed infections. One of the earliest papers to appear was that by Puscairu.[14] In her experience in the treatment of eight patients of gonorrheal ophthalmia "It was found that with this treatment absolutely no irritation or intoxicative symptoms were manifested, and all the cases were clinically cured long before the gonococci disappeared from the smears, so that only a bacteriologic examination could give positive information." Wyler[15] reported on two cases which are of sufficient interest to warrant more than mention: 1. An infant, 7 days old, three days after delivery developed ophthalmia. Treatment: frequent flushing with permanganate 1 to 10,000, later chlorin water, 1 dram to 6 ounces, and instillation of ethylhydrocuprein (optochin) hourly. In ten days the baby opened its eyes, the corneas were clear and "everything as it should be." On the twelfth day the corneas became cloudy and ulcerated and, in spite of every effort, perforated. 2. In a severe type of gonorrheal ophthalmia in a boy, 19 months old, limited to one eye. The cornea became opaque, but did not perforate. He reports two cases of mild vernal catarrh, the symptoms of which were greatly ameliorated by instillations of ethylhydrocuprein. This is a valuable observation, since all other remedies have proved practically inefficacious, except for the transient relief from cocain and epinephrin. H. Davier[16] says that ethylhydrocuprein has a direct chemotherapeutic action on the pneumococcus which is due to a bacteriotropism. He reported eight cases of corneal ulceration, seven of which were promptly cured. Wiener[17] healed a hypopion ulcer in the course of two days by applying the remedy for half a minute every hour for six hours on the first day and for twelve hours on the second day.

In pneumococcic ulcers of the cornea ethylhydrocuprein is said to be a specific. Ramsay[18] treated with success thirty-four patients with a 1 per cent. or 2 per cent. aqueous solution applied as follows: After the floor of the ulcer had been cleansed with a quinin or chinosol lotion the boundaries of the ulcer are defined by fluorescein. A dossel of wool saturated with a 1 per cent. solution of ethylhydrocuprein is kept in firm contact with the ulcer for about two minutes, and a 1 per cent. solution instilled frequently. Kümmel[19] reports seventeen cases of ulcus serpens thus treated, which showed clearly the good effects of the remedy, only one case proving obstinate. Goldschmidt,[20] Stengele[21] and Holth[22] report excellent results in pneumococcic affections. Hansell[23] had phenomenal success in a case of pure pneumococcic ulceration in a patient 3 years of age. The remedy has been employed in suppurative dacryocystitis with good results by Stengele[24] and Posey.[25] Weeks, in a paper read before the American Ophthalmological Society, May, 1916, warns against the indiscriminate use of ethylhydrocuprein internally. Since it is strongly related to quinin its use may cause sudden blindness; he reports such a case.

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[14] Puscariu: Klin. Monatsbl. f. Augenh., 1914, **53,** 342; Ibid., Clin. opht., 1914, **20,** 357.

[15] Wyler: Ann. Ophth., January, 1916.

[16] Davier: Clin. opht., January, 1916.

[17] Wiener: Med. Rec., New York, Jan. 17, 1914.

[18] Ramsay: Glasgow Med. Jour., May, 1915.

Vernal conjunctivitis, also designated by various other names, such as hyperplastic conjunctivitis; fibroma of the limbus; phlyctenula pallida, and vernal catarrh, is not uncommon in the warm months. It attacks principally young persons from 10 to 20 years of age, preferably males, recurs for several years, with entire relief in the cold months, and is attended with intolerable itching. Many remedies have been tried and unsuccessfully; to quote de Schweinitz,[26] "weak astringents and antiseptic lotions; the application of boroglycerid to the everted lid; the systematic use of a preparation of suprarenal extract or of adrenalin chlorid 1 to 10,000; sulphate of quinin; watery solution of ichthyol (1 to 2 per cent.); salicylic ointment, 1 per cent.; massage with yellow oxid ointment; electrolysis; a collyrium of antipyrin (10 per cent.); instillations of a 2 per cent. protargol; Roentgen rays; radium, and the internal administration of arsenic."

It may be inferred that no remedy has been satisfactory. If the etiology were known the benefit of treatment would be more assured. The writer tried ethylhydrocuprein in the case of a young woman who suffered almost intolerably each summer for several years from itching of the lids. She used a 2 per cent. solution, afterward weakened to 1 per cent., three or four times a day, and with this remedy reported that the itching was well controlled.

Wyler[15] reports two cases: Dr. Z., used a 1 per cent. instillation every two hours. "At the end of a week the patient reported absolute comfort from the itching, and he has continued to use this preparation when necessary through the entire summer with perfect relief." The second patient received the same treatment with the same result.

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[19] Kümmel: München. med. Wchnschr., 1914, **61,** 1326.
[20] Goldschmidt: München. med. Wchnschr., 1914, **61,** 1505.
[21] Stengele: Klin. Monatsbl. f. Augenh., 1915, **54,** 446.
[22] Holth: Wchnschr. f. Therap. u. Hyg. d. Auges, 1914, **17,** 295.
[23] Hansell, H. F.: Ophth. Rec., March, 1916.
[24] Stengele: Ann. d'oculist, August, 1914.
[25] Posey, W. C.: Ophth. Rec., June, 1916.
[26] De Schweinitz: Diseases of the Eye, Ed. 8, 1916.

Vernal catarrh may be confused with hay-fever, rose cold and similar acute nasal affections, but has many points of difference, such as duration, gradual onset and decline, and the flat epithelial outgrowths from the conjunctiva that have not been described as having been associated with the nasal affection. The remedy is harmless, and easily applied.

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